# Chapter 10
# Other Specific Outcomes

Sections of this chapter on the health consequences of smoking are accompanied by evidence tables detailing the studies that were used to evaluate the evidence to assess causality. A supplement to this report is provided that contains these tables. The tables included in the supplement are indicated with an "*S*" where they are called out in the text.

# Introduction

This chapter addresses evidence on smoking and health effects over a range of specific diseases and nonspecific but adverse consequences. Previous Surgeon General's reports have reviewed age-related macular degeneration, dental diseases, and diabetes. Since the last reviews were carried out on those topics, additional significant findings have been reported. Building on the reviews in the 2004, 2006, and 2010 reports, this chapter reassesses the state-of-the-evidence for these conditions giving consideration to more recent publications. Smoking and immunity, rheumatoid arthritis and systemic lupus erythematosus, and inflammatory bowel disease are being covered for the first time in this Surgeon General's report.

# Eye Disease: Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is the leading cause of blindness for persons 65 years of age and older in the United States (Congdon et al. 2004). Researchers have sought to identify modifiable risk factors and to test strategies to modify the natural history of AMD, but preventive therapy is not available for early AMD. Located at the center of the optical axis, the macula is a component of the retina and contains the fovea, a highly specialized area that is responsible for high-resolution vision. The retina consists of neural tissues, including photoreceptors, which convert energy from visible light to electrical signals and sends these signals to the brain for processing. Photoreceptors (rods and cones) in the retina have high metabolic requirements; they replace their outer segments daily. The metabolic functions of the retina are supported by retinal pigment epithelium (RPE), which phagocytizes an estimated 25,000–30,000 outer segment membranes per day. This high rate of activity is made possible by an exchange of nutrients and the removal of waste within the retinal blood supply through the choriocapillaris. RPE and its anchor, Bruch's membrane, form a blood-retinal barrier to this exchange. Thus, the complex of choriocapillaris, RPE, and Bruch's membrane serves as the nutritional source for the sensory retina. Researchers hypothesize that AMD stems from changes in each of the tissues in this complex.

AMD is an umbrella term for a variety of degenerative changes in the macula. The disease's early stages are characterized by pigmentary disturbances, development of drusen (deposits of extracellular material), and atrophic changes. The late stages are characterized by RPE atrophy; loss of photoreceptors (which occurs in atrophic AMD or geographic atrophy [GA]); and, less commonly, neovascular (NV) AMD. With NV AMD, new but unstable blood vessels develop in the choroid and grow under or through the RPE via breaks in Bruch's membrane. Leakage from these NV membranes may lead to detachment of RPE, hemorrhage, and the later formation of a disciform scar. The late stages of AMD are associated with loss of vision—classically the loss of central vision, which is critical for such activities as reading and performing near work (such as typing, cooking, and sewing).

With the discovery of highly significant associations between AMD and several complement pathway-associated genes, a coherent story for inflammation as the model for AMD pathogenesis is emerging (Anderson et al. 2010). Morphologic changes associated with AMD include thickening of Bruch's membrane, the formation of basal deposits within Bruch's membrane, and accumulation of drusen. Drusen accumulate within Bruch's membrane in the same area in which basal deposits form. A wide variety of complement-related molecules have been reported in

drusen; some authorities regard these molecules as the byproduct of chronic local inflammatory processes. The dysregulation of the complement cascade is likely an early predisposing step in the development of drusen, but the role of the complement in advanced AMD, either NV or GA, is not yet clear. At least two types of drusen are recognized clinically based on their appearance. Small, hard drusen are a common feature of aging; while large, soft drusen are commonly found with aging, but are also a risk factor for the development of advanced AMD. Drusen can appear and disappear over time, however, making them unstable biomarkers for risk of AMD (Bressler et al. 1995; Klein et al. 1997). Moreover, most persons with large, soft drusen do not develop advanced AMD (Klein et al. 1997), and the epidemiologic patterns associated with advanced AMD may not be the same as those for drusen-defined early AMD. Thus, the specific phenotypes of early AMD that are most likely to progress to NV or GA AMD need further characterization. This lack of specificity should be considered when interpreting evidence of the association between smoking and early versus advanced AMD.

## Conclusions from Previous Surgeon General's Reports

The 2004 Surgeon General's report on smoking and health, based on research available at the time, offered the following conclusions (U.S. Department of Health and Human Services [USDHHS] 2004):

1. The evidence is suggestive but not sufficient to infer a causal relationship between current and past smoking, especially heavy smoking, with risk of exudative (neovascular) age-related macular degeneration.

2. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and atrophic age-related macular degeneration.

## Biologic Basis

The inflammation model of AMD posits that smoking, against a background of genetic susceptibility, leads to changes in RPE, Bruch's membrane, and choroidal endothelium and generates a local inflammatory response (Wang et al. 2009a). This response is dysregulated and ongoing in genetic-susceptible persons who lack appropriate modulating factors, leading to lysis of bystander cells and the development of advanced AMD (Anderson et al. 2010). Oxidative stress is one of the primary proposed mechanisms for smoking-related damage to retinal structures (Rahman and MacNee 1996); cigarette smoke is a strong oxidant, and smoking results in systemic oxidative stress. Immunohistochemical evidence shows oxidative byproducts of photoreceptor fatty acids in the outer segments of photoreceptors in RPE and in autoantibodies to these byproducts in AMD (Gu et al. 2003). Oxidative stress—the result of damage done by free radicals to protein and lipids and, possibly, to DNA—may contribute to cell injury within RPE and apoptosis, a key histopathologic finding in GA AMD (Del Priore et al. 2002). The decreased ability of RPE to phagocytize cellular products leads to the accumulation of debris in Bruch's membrane; this debris interferes with the exchange of nutrients between RPE and the choriocapillaris. Upregulation of the complement alternative pathway is a proposed mechanism for the development of AMD; smoking alters the ability of the *CFH* gene to bind with the *C3* gene, which may activate the alternative pathway of the complement (Kew et al. 1985).

The macula is a particularly attractive target for oxidative stress because of its high exposure to light, high metabolic rate, and high concentrations of fatty acids. But the macula is also rich in antioxidative protective mechanisms, including an array of antioxidant nutrients, and enzymes and melanin. Smoking, however, may increase oxidative stress on the macula by robbing it of its defenses (Hammond et al. 1996) and reducing macular pigment and plasma levels of antioxidants.

Vascular insufficiency may also figure in, or at least be a contributing mechanism to, the pathogenesis of AMD. Changes in the choroidal circulation may impair the ability of RPE to dispose of waste substances, leading to the accumulation of waste material. The rate and volume of blood flow through the choriocapillaris is high in response to the demands of the pigmented epithelium and photoreceptors, but smoking can alter choroidal blood flow (Bettman et al. 1958). Smoking also affects the vasculature through increased platelet adhesions and hypoxia from elevated levels of carboxyhemoglobin, which may add to the stimulation of new vessel growth.

Highly suggestive evidence for a link between smoking and AMD comes from studies of mice exposed to chronic smoke versus those raised in filtered air. In such comparisons, mice exposed to smoke had thicker Bruch's membranes, more basal laminar deposits, and relatively higher percentages of apoptotic RPE cells and immunolabeling for markers of oxidative damage (Wang et al. 2009b; Cano et al. 2010)—all signs of early AMD.

In conclusion, multiple pathways are likely responsible for the degenerative changes in the macula with

age, and a reasonable basis exists for presuming that the effects of smoking may operate through one or more of these pathways.

## Description of the Literature Review

For this update, the National Library of Medicine's PubMed service was used to search for articles about smoking and AMD. The first search yielded 362 results using the terms "macular degeneration" AND "smok*" (limited to English and humans). The second search yielded an additional 280 results using the terms "age-related macular degeneration" OR "senile macular degeneration" OR "age related maculopathy" OR "choroidal neovascularization" (CNV) OR "drusen" OR "geographic atrophy" OR "atrophic macular degeneration" AND ("cigarette" OR "smoking" OR "tobacco" OR "smok*"). Both searches were completed as of March 1, 2010. The reference list of each article was reviewed to determine whether any article had been missed by the two searches. In all, this discussion includes 84 articles that were not used during the previous review by the Surgeon General in 2004.

## Epidemiologic Evidence

In assessing the relationship between AMD and smoking, there are several methodologic issues to be considered. First, advanced AMD occurs primarily in older persons; indeed, an estimated 12% of the U.S. population 80 years of age or older has advanced AMD (Friedman et al. 2004). Second, the life expectancy of smokers is less than that of nonsmokers, and so the selective survival of smokers into the at-risk age range is an issue. Third, because relatively few older smokers could be recruited into studies or otherwise included in these investigations, the power to detect associations with smoking in all but the largest studies is limited. The limited numbers also reduce the power to detect incident cases among smokers in prospective studies and may be a source of bias, because smokers and those with vision loss are often less likely to return for follow-up.

One way to circumvent the problem of studying clinically symptomatic AMD would be to assess the association between smoking and precursor lesions or early AMD, but these earlier stages of AMD are imperfect surrogates for risk of advanced AMD, the outcome of interest. For example, in a large clinical trial, the best predictors of 5-year incidence of advanced AMD were very large areas affected by drusen with increased retinal pigment or a large area of depigmentation with drusen; even eyes affected to this degree, however, had only a 20% chance of progression to advanced AMD within 5 years (Davis et al. 2005). Thus, some risk factors may be misclassified when researchers use early or intermediate AMD lesions as surrogates for advanced AMD, and the associations observed between smoking and early lesions and those between smoking and advanced AMD are unlikely to be consistent.

These potential difficulties notwithstanding, most of the relevant studies have found an increased risk between some measures of smoking and clinical signs of AMD. However, more evidence is available on the association between smoking and intermediate or advanced AMD than on the association between smoking and signs of early AMD, and the specific clinical manifestations of early or intermediate AMD associated with smoking differ among the studies.

Tables 10.1*S*–10.4*S* summarize evidence by type of study: (1) case-control (Table 10.1*S*), (2) cross-sectional (Table 10.2*S*), (3) prospective cohort (Table 10.3*S*), and (4) other types (Table 10.4*S*). Of these various study designs, data from cohort studies are most informative because by repeatedly observing the development of AMD and its precursors, data from prospective cohorts are informative on the association between smoking and AMD across its natural history. The recent wave of case-control studies has focused on identifying genetic determinants of risk for AMD. Of the numerous case-control studies that have been reported, the earliest was conducted in 1979. Some of these studies have small samples and limited statistical power, and the basis for establishing the presence of AMD has differed across the studies. Regardless, most of the studies found significant associations between current or ever smoking and AMD. In addition, dose-response relationships were found with several measures of smoking, including duration and pack-years.[1] Several other studies have not found any such association.

Prospective cohort studies, which have addressed both early and late AMD, offer the most substantial evidence. In one major population-based study (the Beaver Dam Eye Study in Wisconsin), smoking status and pack-years at baseline were not associated with any of the signs of early AMD. However, in the 5-, 10-, and 15-year follow-ups, current smoking at baseline was related to the incidence of large, soft drusen—with significant dose-response relationships observed at the 5- and 10-year follow-ups with pack-years at baseline (Klein et al. 1993, 1998, 2002,

[1]The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

2008a). A population-based cohort study in Australia that used the same system for grading AMD found no relationship between smoking and early signs of AMD at baseline, but at 5-year follow-up reported increased risk for incident retinal pigment abnormalities with current smoking at baseline (but with no dose-response relationship and increased risk was only found among men) (Mitchell et al. 2002). The 10-year follow-up of the same cohort did not confirm this finding (Smith et al. 1996; Mitchell et al. 2002; Tan et al. 2007). A longitudinal study in an older population in Salisbury, Maryland, found that current smoking was a risk factor for progression to large drusen or pigmentary abnormalities (Chang et al. 2008).

For early-stage AMD, several cross-sectional studies have produced relevant but mixed results. One cross-sectional study of Latinos found a relationship between smoking, particularly smoking for 5 or more pack-years, and increased odds of soft drusen (Fraser-Bell et al. 2006). Another cross-sectional study, which included Mexican Americans, did not find a relationship between current smoking and soft drusen (Klein et al. 1999). Other cross-sectional, population-based studies or longitudinal cohort studies have not found any relationship between smoking and early signs of AMD (Delcourt et al. 1998; Arnarsson et al. 2006; Wong et al. 2006; Chakravarthy et al. 2007; Klein et al. 2007; Cackett et al. 2008; Chang et al. 2008; Baker et al. 2009; Coleman et al. 2010). Using smoking status as the only baseline metric makes it difficult to interpret analyses of prospective studies, because smoking status will likely change over time and may need more complex modeling.

Strong evidence from several studies in widely differing populations suggests that smoking is associated with advanced AMD, both NV and GA. In the Australian prospective study, both the baseline results, and the 10-year follow-up, identified an association between current smoking and increased risk of NV AMD and GA AMD (Smith et al. 1996; Tan et al. 2007). A relationship was not found, however, with pack-years. Other cross-sectional, population-based studies have found a dose-response relationship between pack-years of smoking and advanced AMD. Studies in Holland, France, and Singapore, for example, reported increased odds of NV AMD with greater pack-years (Vingerling et al. 1996), and studies in France, Japan, and Singapore related pack-years with advanced AMD (Delcourt et al. 1998; Cackett et al. 2008; Yasuda et al. 2009). Notably, a large case-control study across multiple sites in Europe found increased odds of NV AMD and GA AMD with current smoking and a dose-response relationship between pack-years and NV AMD (Chakravarthy et al. 2007). In the Southeastern United States, a large clinic-based sample of intermediate and severe AMD cases, with ethnically matched controls, found a dose-response relationship between pack-years and intermediate AMD and NV AMD (Schmidt et al. 2005).

Two large prospective cohorts of health professionals in the United States, the Nurses' Health Study (NHS) (women) and the Physicians' Health Study (men), found significantly greater risks of AMD (defined as clinical manifestations of AMD causing loss of vision) associated with increased pack-years (Christen et al. 1996; Seddon et al. 1996). In the NHS, the cases were either NV AMD or GA AMD, while in the Physicians' Health Study, about one-third of AMD cases were advanced. A large case-control study using the United Kingdom General Practice Database identified 18,007 persons with physician-diagnosed AMD (not further specified); these persons were compared to 86,169 controls who were matched for age, gender, and the general practice in which they were enrolled (Douglas et al. 2007). This study found an increased risk of AMD with current smoking (odds ratio [OR] = 1.17; 95% confidence interval [CI], 1.11–1.23) and former smoking (OR = 1.14; 95% CI, 1.09–1.20). These lower risks may reflect the uncertainty of the AMD phenotype in the database. In the United States, a study of male twins found an increased risk of AMD (not further categorized but including advanced AMD and some intermediate grades of AMD) with current smoking that bordered on statistical significance (OR = 1.91; 95% CI, 0.99–3.66) (Seddon et al. 2006a).

In a study of 104 families (also in the United States) in which siblings were discordant for CNV and the normal siblings were past the age of diagnosis of the affected sibling, Kim and colleagues (2008a) found an increased risk of CNV with 10 or more pack-years (OR = 1.97; 95% CI, 1.12–3.46). Another case-control study, this one of persons 75 years of age or older from the Medical Research Council Trial of Assessment and Management of Older People in the Community in the United Kingdom, found a relationship between current smoking and advanced AMD (Evans et al. 2005; Khan et al. 2006). In a study by Khan and colleagues (2006), a total of 40 pack-years or more was associated with increased odds of NV AMD and GA AMD. The Age-Related Eye Disease Study in the United States, a clinical trial of the use of antioxidants and vitamins and the risk of AMD, had a large population of cases with a variety of signs of AMD and an average 6.3 years of follow-up to examine progression to advanced AMD. Incident NV AMD in the Age-Related Eye Disease Study was related to having more than 10 pack-years (OR = 1.55; 95% CI, 1.15–2.09), as was incident central GA AMD (OR = 1.82; 95% CI, 1.25–2.65) (Clemons et al. 2005). The Complications of Age-related Macular Degeneration Prevention Trial looked at the prevention of vision loss in CNV and GA AMD. After

a 5- to 6-year follow-up, the risk of CNV was greater in current smokers (OR = 1.98; 95% CI, 1.16–3.39) than in never smokers; the increased risk was not seen in smokers who had quit at an indeterminate time. The study found a modestly increased risk of GA AMD with current smoking that failed to reach statistical significance (Complications of Age-related Macular Degeneration Prevention Trial Research Group 2008).

Inconsistent findings were observed only in the Beaver Dam Eye Study, the prospective, population-based cohort study in Wisconsin, in which cross-sectional risks for NV AMD were found for both current smoking and total pack-years among women at baseline. The subsequent longitudinal observations failed to confirm the findings (Klein et al. 1993, 1998, 2002, 2008a). Many of the more recent reports have addressed the genetic basis of AMD, including possible genetic determinants of the risk for AMD associated with smoking. As summarized in Tables 10.1*S*–10.4*S*, researchers have accumulated compelling evidence for the relationship of genetic variants to advanced AMD and have identified gene-smoking interactions for advanced AMD. In most of these studies, however, smoking has been categorized as "current," "past," or "never" at best, or as "ever" versus "never." Although smoking is a significant, independent risk factor for advanced AMD, many studies have not found evidence for an interactive effect of smoking with the genetic variants under investigation (Schmidt et al. 2005; Seddon et al. 2006b; Sepp et al. 2006; DeAngelis et al. 2007; Schaumberg et al. 2007; Scott et al. 2007; Tam et al. 2008; Wang et al. 2008a, 2009b,c; Despriet et al. 2009; Park et al. 2009). Smoking is also a risk factor for the progression of AMD (Baird et al. 2008), but many of the studies noted above were underpowered to detect gene-smoking interactions.

Four studies found evidence for an interaction of smoking with a genetic factor in regard to risk for AMD:

- Schmidt and colleagues (2006) investigated the joint effect of smoking and two susceptibility genes for AMD and found that (a) smoking did not increase the risk for AMD in the absence of high-risk genotypes for both genes, and (b) one allele appeared to exert the strongest effect in smokers. However, another study did not find evidence for an interaction with this gene while finding an independent effect of smoking on AMD (Francis et al. 2007).

- Chu and colleagues (2008) found in a Han Chinese population an interaction between being a heterozygote for a variant in the *CFH* gene and smoking and increased risk of NV AMD but not for homozygotes. The null result in homozygotes suggests that the interaction they found might have been statistically significant by chance.

- Tuo and colleagues (2008)—using multiple sources of cases from a clinical trial, case series, and population-based study—found a significant interaction between ever smoking and a variant in the *HTRA1* gene. Together, the risk variant and smoking increased the odds of AMD to 17.71 (95% CI, 7.49–41.88) using never smoking and absence of the risk variant as the referent. The study also found significant independent effects of ever smoking.

- Spencer and colleagues (2007) found a protective effect for intermediate and advanced AMD considered together in smokers with a haplotype spanning the *CFH* gene, but did not observe a main protective effect for the gene per se. The association between smoking and increased risk of AMD was significant in the interaction model.

Taken together, these studies provide strong evidence for a causal relationship between smoking and AMD. Further work is needed on the possible interactions of smoking with high-risk genetic polymorphisms.

The evidence suggests that current smokers have a greater risk of advanced AMD than former smokers, and some studies have found that former smokers have a significantly greater risk of advanced AMD than never smokers (Eye Disease Case-Control Study Group 1992; Christen et al. 1996; Seddon et al. 1996, 2006a; Vingerling et al. 1996; Delcourt et al. 1998; McCarty et al. 2001; Mitchell et al. 2002; Evans et al. 2005; Schmidt et al. 2005; Fraser-Bell et al. 2006; Khan et al. 2006; Chakravarthy et al. 2007; Francis et al. 2007; Tan et al. 2007; Cackett et al. 2008; Complications of Age-related Macular Degeneration Prevention Trial Research Group 2008). The relationship appears to have depended, at least in part, on time since quitting smoking. In cases in which a person had quit smoking for 20 years or more, his or her risk for AMD was no different than that of a never smoker (Christen et al. 1996; Vingerling et al. 1996; Delcourt et al. 1998; Evans et al. 2005; Khan et al. 2006; Chakravarthy et al. 2007), but such risk was elevated in most studies in which quitting time was less than 20 years. In the NHS, risk for AMD did not differ between current smokers and those who had quit smoking for 15 years or more (OR = 0.9; 95% CI, 0.6–1.3) (Seddon et al. 1996). The prospective cohort study in Australia found that, compared with never smokers, the relative risk (RR) of incident GA AMD was 2.9 (95% CI, 0.9–9.4) for those who had quit smoking for 17 years or more and 4.4 (95% CI, 1.2–15.8) for those who had quit smoking for less than 17 years (Tan et al. 2007).

## Evidence Synthesis

The additional findings since the 2004 Surgeon General's report strengthen the evidence that current smoking is associated with advanced AMD, both NV and GA. The association is found across a range of populations and through various study designs. Dose-response relationships have been described, and prospective cohort studies have shown increased risk for both the incidence and progression of AMD. The risk persists across a variety of genetic variants that are strongly associated with AMD. Quitting smoking appears to decrease the risk of AMD, but several decades after quitting smoking, the risk remains higher for former smokers than for never smokers. Quitting for at least 20 years is associated with decreased risk of AMD in a few studies. Results from mouse models further bolster these findings, supporting the biological plausibility of a causal association. In studies in which mice were reared in environments contaminated with smoke, the mice showed histologic retinal changes similar to those observed in persons with AMD. The lack of association between smoking and early AMD in epidemiologic studies may result from misclassification that arose from the imprecise designation of early AMD with resulting bias toward the null. Further work on improving early classification systems is warranted. Smoking may also be related to the progression of AMD to the NV form although not related to the onset of early lesions.

## Conclusions

1. The evidence is sufficient to infer a causal relationship between cigarette smoking and neovascular and atrophic forms of age-related macular degeneration.

2. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of advanced age-related macular degeneration.

## Implications

The role of smoking in causing advanced AMD, which results in loss of vision, is a significant public health concern and a major clinical issue in the United States. The public health burden of AMD will increase because the at-risk population of elderly is growing. Current smoking is a risk factor for advanced AMD and progression of AMD, but further work is needed to determine the extent to which quitting smoking and greater time since quitting smoking attenuate the risk. Because smoking causes both nuclear cataracts (USDHHS 2004) and AMD, it is important for ophthalmologists, optometrists, and other health care providers to assess and address the smoking status of their patients.

# Dental Disease

Diseases of the teeth and their supporting structures have a significant impact on social, economic, and personal well-being. In 2009, more than $102 billion was spent on dental care in the United States (National Center for Health Statistics 2012), and acute dental conditions resulted in an estimated 1.6 million days of missed school and 2.4 million days of lost work annually (USDHHS 2000).

## Conclusions from Previous Surgeon General's Reports

The 2004 Surgeon General's report on the health consequences of smoking reviewed the evidence on the association between active smoking and two major dental diseases: periodontitis and caries. The report concluded that the evidence was sufficient to infer a causal relationship between smoking and periodontitis. Data on the association between smoking and caries were much more limited and inconsistent. Thus, the 2004 report concluded that the evidence was insufficient to infer the presence or absence of a causal relationship between smoking and coronal caries (caries affecting the crown and not the root portion of the tooth). The report also concluded that the evidence was suggestive but not sufficient to infer a causal relationship between smoking and caries of exposed root surfaces.

This section updates the earlier review, covering the full scope of evidence on the relationships between active and passive smoking and dental caries through 2011. It also considers associations between smoking and dental implants through 2010.

## Smoking and Dental Caries

Dental caries is a multifactorial disease marked by the localized destruction of susceptible hard tissues by acidic byproducts from bacterial fermentation of dietary carbohydrates (Selwitz et al. 2007). The disease process starts with microbiological shifts in the complex bacterial biofilm (dental plaque) that covers the surface of a tooth. The incidence of dental caries is affected by the flow and composition of saliva, exposure to fluoride, consumption of dietary sugars, and patterns of preventive behaviors (e.g., daily brushing with fluoride toothpaste). If left untreated, caries can lead to incapacitating pain, bacterial infection that leads to pulpal necrosis, tooth extraction, loss of dental function, and even acute systemic infection.

To measure the prevalence of dental caries affecting the enamel covered crowns of the teeth, most epidemiologic studies conducted during the past 70 years have used some variation of the DMF index (Klein et al. 1938), a count of the number of permanent teeth that are decayed (D), missing due to caries (M), or filled (F). The DMF index is a measure of disease severity, not just the prevalence of caries. The DMF index has its variants: DMFT, for which "T" stands for "permanent teeth"; and DMFS, for which "S" stands for tooth surfaces. The "M" component of the index may be omitted in adult studies because of the uncertainty as to why a tooth is missing; therefore, some studies report DFT or DFS scores. Other studies report the components of DMFT individually, such as DT, FT, and MT. Root-surface caries (R) is almost always scored and reported separately from coronal caries and is usually designated as RDFS or RDS (the "M" component is not reported for root-surface caries). For primary teeth (i.e., deciduous teeth or baby teeth), the index uses lowercase letters to designate teeth or tooth surfaces that are decayed, missing due to dental caries, or filled (i.e., dmft or dmfs).

### Biologic Basis

Several mechanisms support a possible causal association between active smoking and dental caries. Perhaps the most consistent explanation, other than causation among studies that have found a relationship between smoking and caries, is that smokers tend to practice less frequent or less effective oral hygiene and plaque removal (Preber and Kant 1973; Macgregor and Rugg-Gunn 1986; Andrews et al. 1998).

Findings on biological mechanisms also offer explanations for associations between smoking and caries. Several studies found that active smoking might lower the pH or reduce the buffering capacity of saliva (Heintze 1984; Parvinen et al. 1984), which could impair its function as a protective factor against demineralization of tooth enamel (Edgar and Higham 1996). In contrast, however, one review concluded that smoking increases the flow rate of saliva (Macgregor 1989), which raises pH and increases the calcium concentration of saliva (ten Cate 1996). These factors tend to favor remineralization of the enamel. Thus, smoking may actually exert a protective effect against caries. Overall, the evidence is inconclusive as to whether smoking plays a major role in the impairment of salivary function that would be relevant to the development of dental caries.

Investigators also offer several hypotheses for the biological mechanisms through which maternal smoking and exposure to secondhand smoke may increase the risk for dental caries in children. Based on an in vitro study that found tobacco extract promotes the growth of cariogenic *Streptococcus mutans* (Lindemeyer et al. 1981) and studies that suggested cariogenic bacteria are transmittable in saliva from mother to infant (Ettinger 1999). Aligne and colleagues (2003) speculated that mothers who smoke may be more likely than nonsmoking mothers to transmit cariogenic bacteria to their children. Aligne and colleagues (2003) speculated that the immunosuppressive properties of secondhand tobacco smoke (Edwards et al. 1999) may increase the risk for dental caries. In addition, some evidence indicates that maternal smoking during pregnancy may disturb tooth formation in infants (Heikkinen et al. 1997) and could increase later susceptibility to dental caries (Ayo-Yusuf et al. 2007).

Behavioral factors may also affect the association between active or secondhand smoke and caries; such an association may be partly due to lower rates of dental care utilization among smokers than nonsmokers in many developed nations (Mucci and Brooks 2001; Netuveli et al. 2006; Yusof et al. 2006; Millar and Locker 2007; Ohi et al. 2009). In particular, differences in patterns of seeking dental care by smoking status may partially explain why smokers may be more likely than nonsmokers in some studies to have untreated caries but less likely to have evidence of treated disease.

### Description of the Literature Review

The 2004 Surgeon General's report on the health consequences of smoking included a review of epidemiologic studies from the National Library of Medicine's PubMed database published in the English language from 1965–2000 (USDHHS 2004). This review updates that 2004 report by using the same Medical Subject Headings (MeSH) ("smoking," "tobacco," "dental caries," and "tooth demineralization") to search for English-language articles

published from 2000–2011. Reference lists from published studies and review articles were searched to identify additional studies not in PubMed.

## Epidemiologic Evidence

### *Active Smoking and Dental Caries*

Table 10.5*S* summarizes the findings from 14 cross-sectional studies, 1 cohort study, and 1 case-control study published between 2005–2011 that met the selection criteria for this report. These 16 studies were conducted in 11 countries. Of the 14 cross-sectional studies, 4 studies (Dye et al. 2007; Ojima et al. 2007; Iida et al. 2009; Skudutyte-Rysstad et al. 2009) presented data on the estimated proportion of the population that had untreated decay at the time of the survey. Two cross-sectional studies (Dye et al. 2007; Du et al. 2009) reported the proportion of the population that had experienced either treated or untreated dental caries at some time. The five studies that presented prevalence data by smoking status (Dye et al. 2007; Ojima et al. 2007; Du et al. 2009; Iida et al. 2009; Skudutyte-Rysstad et al. 2009) found a significantly greater prevalence of untreated caries among current smokers than never smokers. In a nationally representative survey of the U.S. population, Dye and colleagues (2007) found no significant difference by smoking status in the prevalence of experience with caries among adults, but prevalence was very high for all groups (91.2–92.8%). Ten of the 14 cross-sectional studies presented data for some variation or component of the DMF index: 8 of the studies separately considered the mean number of DT or DS (in addition to reporting on DMFT or DMFS), and 2 of the studies reported on only mean DMFT or DMFS. Seven of the 8 studies that reported data on mean DT or DS found a significantly higher mean number of DT or DS among current smokers than among nonsmokers (Birnboim-Blau et al. 2006; Dye et al. 2007; Hamasha and Safadi 2008; Roberts-Thomson and Stewart 2008; Vellappally et al. 2008; Kumar et al. 2010; Campus et al. 2011); 1 study found no difference in mean DT by smoking status (Aguilar-Zinser et al. 2008). However, in 3 of the 7 studies (Birnboim-Blau et al. 2006; Dye et al. 2007; Hamasha and Safadi 2008) that found a significant higher mean number of DT or DS among current smokers than nonsmokers, current smokers also had significantly fewer filled teeth or tooth surfaces and significantly more missing teeth or tooth surfaces than nonsmokers. Such a pattern suggests that some of the differences in the severity of caries between smokers and nonsmokers may be due to differences in their utilization of dental services rather than differences in rates of disease.

In the one cohort study, a 3-year prospective Swedish study of girls 12 years of age at baseline (Bruno-Ambrosius et al. 2005), girls who smoked in eighth grade (the end of the second year of the study) experienced significantly higher 3-year increments in DMFS than girls who did not smoke (7.7 versus 1.9; $p < 0.001$).

In the one case-control study, Ditmyer and colleagues (2010) identified case and control groups from the same cross-sectional survey. This study compared the odds of current smoking among adolescents with four or more DMFT (case group) with the odds of current smoking among those with no history of caries in their permanent dentition (control group). Adolescents in the case group were significantly more likely than those in the control group to be current smokers (OR = 1.85; 95% CI, 1.68–2.06).

### *Secondhand Smoke and Dental Caries*

Previous reports from the Surgeon General have not reviewed the possible association between dental caries and secondhand smoke. To establish the literature base for this review, investigators searched the PubMed database for English-language papers that were published on the topic from 1965–2011. The search used the following MeSH keywords: "tobacco smoke pollution" and "dental caries." Reference lists from published studies and review articles were also searched to identify studies not in PubMed.

The search identified 15 published articles; 3 were excluded because they were either short summaries of an original article published in another journal or were a letter to the editor about a published study. One additional study on the exposure to secondhand smoke and dental caries was identified in the literature search for active smoking and caries. Thus, 13 studies were included in this review (Table 10.6*S*).

Of the 13 studies, 11 used a cross-sectional study design, 1 was a case-control study based on a cross-sectional survey, and 1 was a prospective cohort study. The studies were conducted in seven countries. Most of the studies classified children's exposure (or presumed exposure) to secondhand tobacco smoke by using self-reports from parents or guardians. Most studies defined exposure to secondhand smoke as the presence of one or more smokers in the child's home, but 1 study (Ditmyer et al. 2010) defined it simply as exposure to secondhand smoke. In the study by Aligne and colleagues (2003), children's exposure to secondhand tobacco smoke was based on their level of serum cotinine. Although the studies used a range of case definitions for dental caries, they consistently found that caries were more common among children exposed to secondhand tobacco smoke than among those not exposed, at least for primary dentition.

### Evidence Synthesis

The 2004 Surgeon General's report identified 15 studies, published from 1952–1999, that explored the association between smoking and dental caries (USDHHS 2004). Since that review (i.e., from 2000–2011), 16 additional epidemiologic studies were published on this association, thus greatly expanding the extent of the evidence. The literature consistently suggests that smokers experience a greater prevalence of dental caries and have a higher DMF index than persons who have never smoked. Compared with earlier studies, the more recent studies have consistently adjusted for potential confounders. The findings of some cross-sectional studies indicate a dose-response relationship between smoking and dental caries, with the prevalence of caries generally rising with increasing daily consumption of cigarettes (Aguilar-Zinser et al. 2008; Campus et al. 2011).

However, the patterns of untreated and treated disease suggest that at least some portion of the observed difference may be attributable to such factors as differential use of dental services and other health behaviors. In industrialized nations, dental caries and cigarette smoking are more prevalent among persons in lower socioeconomic status (SES) groups than those in higher SES groups (Dye et al. 2007; Centers for Disease Control and Prevention [CDC] 2010). SES is a strong correlate of factors—such as diet, use of dental services, and oral hygiene practices—that affect dental caries status (USDHHS 2000). Several studies found that decayed or missing teeth are more prevalent among smokers but that restored teeth are more common among nonsmokers (Birnboim-Blau et al. 2006; Dye et al. 2007; Hamasha and Safadi 2008). This pattern for dental caries is consistent with differences between smokers and nonsmokers in their use of dental care or the type of care received, which could account for at least some of the observed differences in caries status between the two groups. According to a nationally representative survey of adults in the United States, current smokers are much less likely than never smokers to have seen a dentist during the preceding 12 months (Dye et al. 2007). According to the 2009 National Health Interview Survey, the proportion of persons who received dental care during the preceding year was strongly associated with SES, with estimates ranging from 39% of those living below the federal poverty level to 77.5% of those living at or above 400% of the federal poverty level (National Center for Health Statistics 2011). Beyond SES differences in the use of dental care, many oral health-related behaviors differ between smokers and nonsmokers. For example, compared with nonsmokers, smokers tend to practice less frequent or less effective oral hygiene and plaque removal (Andrews et al. 1998; Hellqvist et al. 2009).

Similarly, significant behavioral differences between smokers and nonsmokers may increase their children's risk for dental caries, complicating any causal interpretations of the evidence on secondhand smoke and caries. For example, in a study of 3- and 5-year-old children in Belgium, Leroy and colleagues (2008) reported that such practices as applying sugary substances to pacifiers, "cleaning" a pacifier in the parent's mouth, and giving the child sugar-containing beverages between meals are more common among parents who currently smoke than among those who do not. That study adjusted for multiple potential confounders in its analysis and still found a significant association between current smoking and dental caries in the 5-year-old children and a doubling in risk in the 3-year-old children, but the latter finding failed to reach significance (OR = 1.98; 95% CI, 0.68–5.76). Even so, the large number of socioeconomic and behavioral differences in the study between parents who smoked and those who did not raises the possibility of residual confounding of the association between exposure to secondhand tobacco smoke and dental caries despite the authors' use of multivariable regression analysis.

### Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between active cigarette smoking and dental caries.

2. The evidence is suggestive but not sufficient to infer a causal relationship between exposure to tobacco smoke and dental caries in children.

### Implications

In developed nations, smoking is strongly associated with sociodemographic characteristics and a wide range of health behaviors that also are strongly associated with elevated risk for caries. Given the public health importance of dental caries, further research on smoking is needed with careful attention to confounding.

## Smoking and the Failure of Dental Implants

A dental implant is an artificial tooth root that supports restorations to replace one or more missing teeth. A variety of dental implant systems that rely on surgical implantation in alveolar bone are available commercially. Endosseous implants are used most frequently. Although the size, shape, and coating of endosseous dental implants vary, the majority anchor the implant to the bone through

osseointegration. Osseointegration is a direct structural connection at the light microscopic level between bone and the surface of the implant (Brånemark 1985). Most osseointegrated dental implants are manufactured from pure titanium or titanium alloy, and the surface of the implant may be roughened by manufacturing processes or coated by various substances to achieve better integration with the bone.

Because no soft tissue or periodontal ligament is detectable at the interface between the implant and bone, the biologic mechanism of anchoring differs between natural tooth roots, where anchoring relies on both the soft tissue and the ligament(s), and dental implants, where anchoring is achieved by osseointegration. Strong evidence indicates that smoking is a risk factor for the destruction of hard and soft tissue around natural teeth (Bouclin et al. 1997; USDHHS 2004; Palmer et al. 2005; Bergstrom 2006; Warnakulasuriya et al. 2010). Thus, smoking may increase the risk for failure of dental implants (Hinode et al. 2006; Baig and Rajan 2007; Strietzel et al. 2007). This topic has not been reviewed in previous Surgeon General's reports.

## Biologic Basis

Several mechanisms likely increase the risk for the failure of dental implants as a result of smoking. First, smoking is an established cause of periodontitis (USDHHS 2004), and a growing body of literature suggests that smoking may be a risk factor for peri-implantitis (inflammation that affects the bone supporting the implant) and bone loss (Strietzel et al. 2007; Heitz-Mayfield 2008; Renvert and Persson 2009).

The mineralization of the bone adjacent to the implant surface is crucial to the stability and success of osseointegrated implants. Early failures of dental implants may result from an inability to establish an intimate bone-implant contact (Esposito et al. 1998). Localized infection and impaired wound healing are two factors that can lead to such failures; both are associated with smoking (Shibli et al. 2010). Furthermore, peri-implantitis may disrupt the bond between the implant and surrounding mineralized tissue after the establishment of osseointegration; this could lead to late implant failure (Esposito et al. 1998). In addition, smokers tend to experience more peri-implant bone loss than nonsmokers (Strietzel et al. 2007).

## Description of the Literature Review

To establish the literature base on this topic for the present review, investigators searched the PubMed database for studies that were published through December 2010. This search used the following MeSH keywords: "dental implants" or "dental implants, single-tooth" and "smoking" or "tobacco smoke pollution." In addition, reference lists from published studies and review articles were searched to identify studies not in PubMed. To be included, studies had to be original investigations that had implant survival or failure as outcomes and reported those outcomes by smoking status.

## Epidemiologic Evidence

Of the 69 studies included in this review, 40 were classified as retrospective cohort studies, nearly all of which were based on reviews of clinical records (Table 10.7*S*). The remaining studies were either prospective cohort studies or clinical trials that included information about smoking status at baseline.

In most of the studies, patients received multiple dental implants, and the number of implants placed per patient varied widely. Most studies, however, reported outcome data with the implant as the unit of analysis, with analyses generally ignoring the clustering of implants within individuals. Few studies reported failure rates (the number of failures per implant month at risk), but they generally reported the number or proportion of implants that failed. Some studies reported the proportion of individuals who experienced one or more failed implants. Few studies reported estimates of epidemiologic parameters (e.g., RR) that would readily allow cross-study comparisons of the relative proportions of implants that failed among smokers and nonsmokers. Consequently, for most studies, the authors of the present report calculated a crude estimate of RR based on data included in the published paper.

Of the 69 studies, 58 (84%) found that smokers experience a higher proportion of implant failures than nonsmokers. However, the differences in proportions were statistically significant in just 28 (40.6%) of the 69 studies, per the test statistics reported by the authors of the original studies or through the crude confidence limits of parameter estimates calculated for this report (i.e., the 95% confidence limits of crude OR or RR estimates excluded 1.0).

Several studies estimated hazard ratios (HRs) using multivariable models that adjusted for potential confounders (Wilson and Nunn 1999; Berge and Gronningsaeter 2000; Eckert et al. 2001; Chuang et al. 2002; Baelum and Ellegaard 2004; Woo et al. 2004; Ellegaard et al. 2006; Al-Nawas et al. 2007; Balshe et al. 2008; Holahan et al. 2008). In the majority of these studies, smokers had significantly higher HRs than nonsmokers.

### Evidence Synthesis

This review included 69 epidemiologic studies on the association between smoking and failure of osseointegrated dental implants; 49 (62%) of these studies were published from 2001–2009. Most of the studies were methodologically weak and potentially affected by selection bias, uncontrolled confounding, low statistical power, or analytic approaches that ignored clustering effects. Nevertheless, the large majority of studies found that smokers experience a greater proportion of implant failures than nonsmokers. All 10 of the cohort studies that adjusted for potential confounders found higher HRs for smokers (Wilson and Nunn 1999; Berge and Gronningsaeter 2000; Eckert et al. 2001; Chuang et al. 2002; Baelum and Ellegaard 2004; Woo et al. 2004; Ellegaard et al. 2006; Al-Nawas et al. 2007; Balshe et al. 2008; Holahan et al. 2008).

Several published meta-analyses (not shown in Table 10.7*S*) have included subsets of the studies included in this review. For example, Hinode and colleagues (2006) pooled 19 prospective or retrospective cohort studies and calculated an overall OR of 2.17 (95% CI, 1.67–2.83) for the association between smoking and implant failure. Similarly, Strietzel and colleagues (2007) calculated a summary OR of 2.25 (95% CI, 1.96–2.59) in their meta-analysis of 29 cohort studies. Finally, Klokkevold and Han (2007) conducted a systematic review and meta-analysis of 14 studies, finding a pooled difference in the cumulative survival of implants that was 2.68% (95% CI, 1.10–4.26%) lower in smokers than in nonsmokers.

### Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and failure of dental implants.

### Implications

The existing evidence suggests that smoking may compromise the prognosis for osseointegrated dental implants. Thus, an intervention to discontinue tobacco use should be part of the treatment plan for persons who are considering a dental implant.

## Diabetes

This section addresses type 2 diabetes mellitus. The prevalence of type 2 diabetes in the United States has increased dramatically during the past few decades, in parallel with the rapid rise in the country's prevalence of overweight and obesity. According to CDC (2011), 25.8 million Americans, or 8.3% of the population, had diabetes in 2010. About 1.9 million new cases of diabetes, mostly type 2, are diagnosed in U.S. adults (CDC 2011). The raw and age-adjusted prevalence of diabetes is substantially higher in minority populations. Among persons 20 years of age and older in 2007–2009, the non-age-adjusted prevalence of diabetes was 12.6% for non-Hispanic Blacks, 11.8% for Hispanics, 8.4% for Asian Americans, and 7.1% for non-Hispanic Whites (CDC 2011). Diabetes is a leading cause of cardiovascular mortality. Nearly two-thirds of people with diabetes die of cardiovascular disease (Nathan et al. 1997). Diabetes is also the leading cause of new cases of blindness, kidney failure, and nontraumatic lower-limb amputation (CDC 2011). Beyond its unfortunate consequences for quality of life, the economic cost of diabetes is high. In 2007, the estimated total cost of diagnosed diabetes in the United States was $174 billion, including $116 billion from direct medical costs and $58 billion from three indirect costs: disability, work loss, and premature mortality (CDC 2011).

A growing body of evidence from epidemiologic studies suggests that smoking is associated with increased risk of type 2 diabetes (Willi et al. 2007), and studies of pathogenesis also support a potential causal relationship between smoking and diabetes (Xie et al. 2009). However, type 2 diabetes is multifactorial in etiology. The rising prevalence worldwide is generally attributed to increasing overweight and obesity, which is now an important concern in both high- and low-income countries. In many high-income countries, the prevalence of diabetes has risen even as smoking rates have dropped (Chen et al. 2012).

The 2010 Surgeon General's report (USDHHS 2010) reviewed the evidence on the role of smoking in diabetes. This chapter reviews evidence on the association between active smoking and the incidence of diabetes and evaluates the extent to which the evidence supports a causal relationship between smoking and that disorder. Because of limited evidence, this chapter will not review the evidence on the effects of passive smoking on diabetes, the adverse effects of smoking on the development of

diabetic complications, or the benefits of smoking cessation among people with diabetes. These topics were discussed in a comprehensive review by Tonstad (2009).

## Biologic Evidence

Several biologic mechanisms may explain an association between cigarette smoking and the incidence of type 2 diabetes. First, although smokers tend to be leaner than nonsmokers, many epidemiologic studies have shown that smoking is independently associated with an increased risk of central obesity (Barrett-Connor and Khaw 1989; Shimokata et al. 1989; Visser et al. 1999; Canoy et al. 2005). Central obesity is a well-established risk factor for insulin resistance and diabetes. The accumulation of visceral adipose tissue is influenced by the concentration of cortisol (Pasquali and Vicennati 2000), and smokers tend to have higher concentrations of fasting plasma cortisol than nonsmokers (Cryer et al. 1976; Friedman et al. 1987), which might be a consequence of the stimulation of sympathetic nervous system activity induced by smoking (Grassi et al. 1992, 1994). In addition, the differential effects of tobacco smoking on sex hormones may help to explain the positive association between smoking and the central accumulation of fat. Smoking has independent effects on estrogens and androgens in women (Michnovicz et al. 1986; Barrett-Connor and Khaw 1987; Friedman et al. 1987; Khaw et al. 1988) (also see the "Breast Cancer" section of Chapter 6, "Cancer") and decreases plasma testosterone in men (Meikle et al. 1988). These effects may promote the accumulation of abdominal fat, especially in men.

Second, smoking increases inflammatory markers (Arnson et al. 2010) and oxidative stress (Morrow et al. 1995) and impairs endothelial function (USDHHS 2004, 2006, 2010). These mechanisms have been strongly implicated in the development of insulin resistance and irregularities in glucose metabolism (Maritim et al. 2003; Dandona et al. 2004; Potenza et al. 2009).

Third, human experiments using the glucose-clamp technique have found that acute infusion of nicotine aggravates the insulin resistance status in people with type 2 diabetes (Axelsson et al. 2001). Furthermore, cigarette smoking clearly worsens metabolic control, and people with diabetes who smoke require a larger dose of insulin to achieve a level of metabolic control similar to that of nonsmokers (Madsbad et al. 1980). These findings indicate that people with diabetes may be particularly susceptible to the detrimental effects of smoking on insulin resistance (Berlin 2008; Chiolero et al. 2008).

Finally, human and animal studies have found that functional nicotinic receptors are present on pancreatic islet and beta cells, and nicotine can, at least in part, reduce the release of insulin through neuronal nicotinic acetylcholine receptors on islet cells (Yoshikawa et al. 2005). Moreover, several studies in animal models have revealed that exposure to nicotine, particularly in the prenatal or neonatal phases of life, can cause dysfunction of beta cells and increase beta-cell apoptosis, which is mediated via the mitochondrial and/or death receptor pathway (Holloway et al. 2005; Bruin et al. 2007, 2008; Somm et al. 2008).

Thus, taken together, multiple lines of evidence from animals and humans strongly support the hypothesis that cigarette smoking and exposure to nicotine can adversely affect insulin action and the function of pancreatic cells, both of which play fundamental roles in the pathogenesis of diabetes (Xie et al. 2009).

## Epidemiologic Evidence

### Description of the Literature Review

This systematic review and meta-analysis updates the literature from the 2007 review and meta-analysis by Willi and colleagues (2007) covering the association between active smoking and type 2 diabetes. The present review examined articles published between May 2007 (the cutoff date for the paper by Willi and colleagues [2007]) and January 2010. Using the same strategy as that employed by Willi and colleagues (2007), articles were identified through a search of PubMed and Embase. The search incorporated MeSH terms across three themes: smoking or cigarette; diabetes mellitus or glucose metabolism irregularity; and studies with a prospective design. For inclusion in the meta-analysis, studies had to meet several criteria:

- Report data from an original study (i.e., not just review articles)
- Focus on an adult population (i.e., 16 years of age or older)
- Incorporate level of smoking intensity or exposure to nicotine as a primary predictor or one of the cofactors for risk of diabetes, not just as a covariate or confounder

Studies were excluded if they met any of the following conditions:

- Included participants with previously diagnosed diabetes at the beginning of the study

- Used inappropriate comparison groups (i.e., a comparison group other than nonsmokers or former smokers)

- Could not provide original data after inquiries from investigators

If data from a study were reported in several publications, the most relevant or most recent publications were used to avoid double counting.

### *Methods*

The present review abstracted and reviewed 25 studies (Cassano et al. 1992; Perry et al. 1995; Rimm et al. 1995; Kawakami et al. 1997; Njølstad et al. 1998; Sugimori et al. 1998; Uchimoto et al. 1999; Manson et al. 2000; Nakanishi et al. 2000; Strandberg and Salomaa 2000; Hu et al. 2001; Wannamethee et al. 2001; Will et al. 2001; Montgomery and Ekbom 2002; Sawada et al. 2003; Carlsson et al. 2004; Eliasson et al. 2004; Sairenchi et al. 2004; Foy et al. 2005; Lyssenko et al. 2005; Patja et al. 2005; Tenenbaum et al. 2005; Waki et al. 2005; Houston et al. 2006; Meisinger et al. 2006) from the meta-analysis by Willi and colleagues (2007). Two of the 25 studies (Cassano et al. 1992; Sawada et al. 2003) were excluded from the present review because smoking was used as only a confounder for risk of diabetes. The study by Perry and colleagues (1995) was also excluded, because similar results were reported in a later report (Wannamethee et al. 2001).

This review also abstracted and included 21 new studies (Burke et al. 2007; Cugati et al. 2007; Dehghan et al. 2007; Holme et al. 2007; Hur et al. 2007; Mozaffarian et al. 2007, 2009; Onat et al. 2007; Schulze et al. 2007; Hayashino et al. 2008; Lyssenko et al. 2008; Magliano et al. 2008; Nagaya et al. 2008; Nichols et al. 2008; Park et al. 2008; Chien et al. 2009; Cho et al. 2009; Cullen et al. 2009; Hippisley-Cox et al. 2009; Laaksonen et al. 2010; Yeh et al. 2010) that were not part of the meta-analysis by Willi and colleagues (2007). In addition, based on a careful review of reference lists from all relevant publications, 3 studies published before 2007 (Keen et al. 1982; Bonora et al. 2004; Harding et al. 2006) were included. Therefore, this updated meta-analysis included 46 studies about active smoking and risk of type 2 diabetes.

## Study Characteristics

Table 10.8*S* depicts the characteristics of the 51 studies that were selected for the present meta-analysis. All were prospective cohort studies: 44 reported the incidence of diabetes as the sole outcome of interest, and 2 reported the incidence of diabetes plus impaired glucose tolerance (Carlsson et al. 2004; Houston et al. 2006). The association between smoking and risk of diabetes was the primary focus of 27 studies, and smoking was included as one of the cofactors in the other 19 studies.

The diagnosis of diabetes was ascertained by biologic measures in 28 studies, reported by patients or physicians in 11 studies, and determined by other methods (e.g., examination of hospital medical registries and insurance registries) in 7 studies. Because the definition of diabetes and the cutoff points used to establish its presence changed from 1980–2009, the fasting glucose thresholds varied across studies (15 studies did not explicitly describe criteria for this threshold):

- 140 milligrams (mg)/deciliter (dL) (7.8 millimoles per liter [mmol/L]) or higher for 6 studies

- 126 mg/dL (7.0 mmol/L) or higher for 20 studies

- 120 mg/dL (6.6 mmol/L) or higher for 1 study

- 110 mg/dL (6.1 mmol/L) or higher for 3 studies

- 100 mg/dL (5.6 mmol/L) or higher for 1 study

The meta-analysis included more than 3.9 million participants and 140,813 cases of diabetes, with the number of participants in the studies ranging from 241 to 2,540,753. Follow-up ranged from 3.5–30 years, with a median of 10 years. Two studies included only women, 13 included only men, and the remaining 31 included both men and women. Among these 31 studies, 6 reported results for both genders and for the total population, and 5 studies reported results separately by gender.

The studies in the meta-analysis adjusted for many risk measures, such as:

- Age (42 studies)

- Body mass index (33 studies)

- Intensity of physical activity (28 studies)

- Level of alcohol consumption (24 studies)

- Heredity or family history of diabetes (19 studies)

- Gender (19 studies)

- Level of education (13 studies)

- Diet (11 studies)

- Waist circumference or waist-to-hip ratio (11 studies)
- Race or ethnicity (6 studies)

Finally, statistical models in 24 of the studies controlled for biomarkers, such as fasting glucose, insulin, and lipid profile.

### Risk of Diabetes: Smokers Compared With Nonsmokers

Based on 51 comparisons from the 46 studies, active smokers had an increased risk of developing type 2 diabetes compared with nonsmokers, with a pooled RR of 1.37 (95% CI, 1.31–1.44) (Figure 10.1). There was evidence of heterogeneity of the RRs across studies (Q statistic = 273.1; P <0.001; $I^2$ = 82%) that was statistically significant, given the extremely large number of participants in the analysis. Among the 51 comparisons, 40 showed a significantly increased risk of diabetes among smokers, 10 showed a nonsignificant association between smoking and risk of diabetes (in 8 of these studies the RR exceeded 1.00; in 2 it did not), and 1 showed a significant inverse association between smoking and risk of diabetes.

The pooled risk changed little (RR = 1.42; 95% CI, 1.34–1.51) when the two largest studies, which may have dominated the results (Will et al. 2001; Hippisley-Cox et al. 2009), were excluded in a sensitivity analysis (results not shown in a table or figure).

The Begg funnel plot was used to evaluate publication bias (Begg and Mazumdar 1994; Egger et al. 1997). Visual inspection revealed asymmetry and the possibility of publication bias, although the finding was not significant (p = 0.552) (Figure 10.2A). Therefore, a sensitivity analysis was conducted using the trim-and-fill procedure, which conservatively imputes studies to mirror the positive studies that cause asymmetry in funnel plots (Figure 10.2B). The pooled RR incorporating the imputed studies remained significant (RR = 1.26; 95% CI, 1.21–1.33).

### Subgroup Analysis

To explore potential heterogeneity, analyses were stratified by several key study characteristics and clinical factors (Table 10.9). In each stratified analysis, smokers demonstrated a significantly increased RR for diabetes. The quality of the study characteristics did not influence the results substantially. A stronger association between smoking and incident diabetes was found in studies in which blood glucose was measured to assess the presence of diabetes at baseline and endpoint, compared with studies that relied on reports by patients or physicians or on registry data. Studies that used higher fasting glucose thresholds as the definition of diabetes also showed a stronger association between smoking and diabetes.

### Dose-Response Analysis

To generate pooled estimates for the dose-response analysis, the meta-analysis examined studies in which measures of association were stratified by level of smoking intensity. These levels were categorized as never, former, light (0–19 cigarettes smoked/day in most studies; 0–15 cigarettes/day in some studies), and heavy (20 or more cigarettes/day in most studies; 15 or more in some studies). As shown in Table 10.9 and Figure 10.3, the RR increased with higher levels of smoking intensity. When compared with never smokers, former smokers had an RR of 1.14 (95% CI, 1.09–1.19). Compared with nonsmokers, light smokers had an RR of 1.25 (95% CI, 1.14–1.37), and heavy smokers had an RR of 1.54 (95% CI, 1.40–1.68).

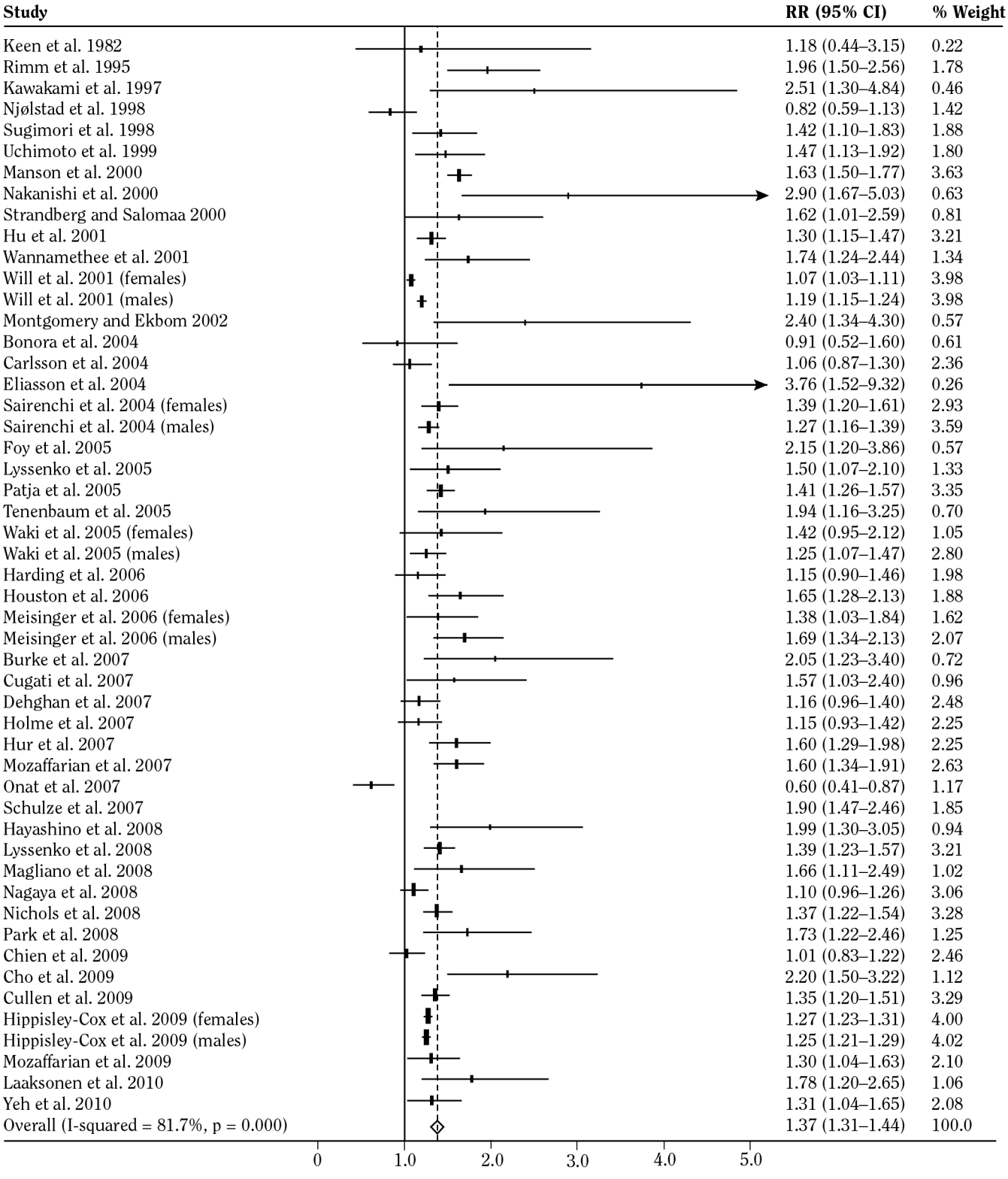
### Smoking Cessation

A review by Filozof and colleagues (2004) found that smoking cessation improves insulin sensitivity in spite of short-term weight gain. In the Atherosclerosis Risk in Communities Study, the risk of incident type 2 diabetes for short-term quitters was above that for current smokers, but it then decreased to the level of never smokers at 12 years (Yeh et al. 2010). Another large cohort study found that smoking cessation reduced RRs for diabetes to those for never smokers after 5 years for women and 10 years for men (Will et al. 2001). Finally, a cohort study from Korea (Hur et al. 2007) showed that smoking cessation is followed by a decreasing risk of diabetes that reaches that of never smokers in the long term.

## Summary

Consistent with the meta-analysis of 25 studies published before 2007 (Willi et al. 2007), the results from this updated meta-analysis provide compelling evidence that active smoking increases risk of developing type 2 diabetes. The association persisted and remained significant in all stratified analyses by various study and participant characteristics. Furthermore, the meta-analysis revealed a clear dose-response relationship—that is, risk of diabetes increases with increasing levels of smoking intensity. The variety of potential confounding factors considered and the finding of a dose-response relationship weigh against the possibility of residual confounding as the explanation for the association between smoking and diabetes.

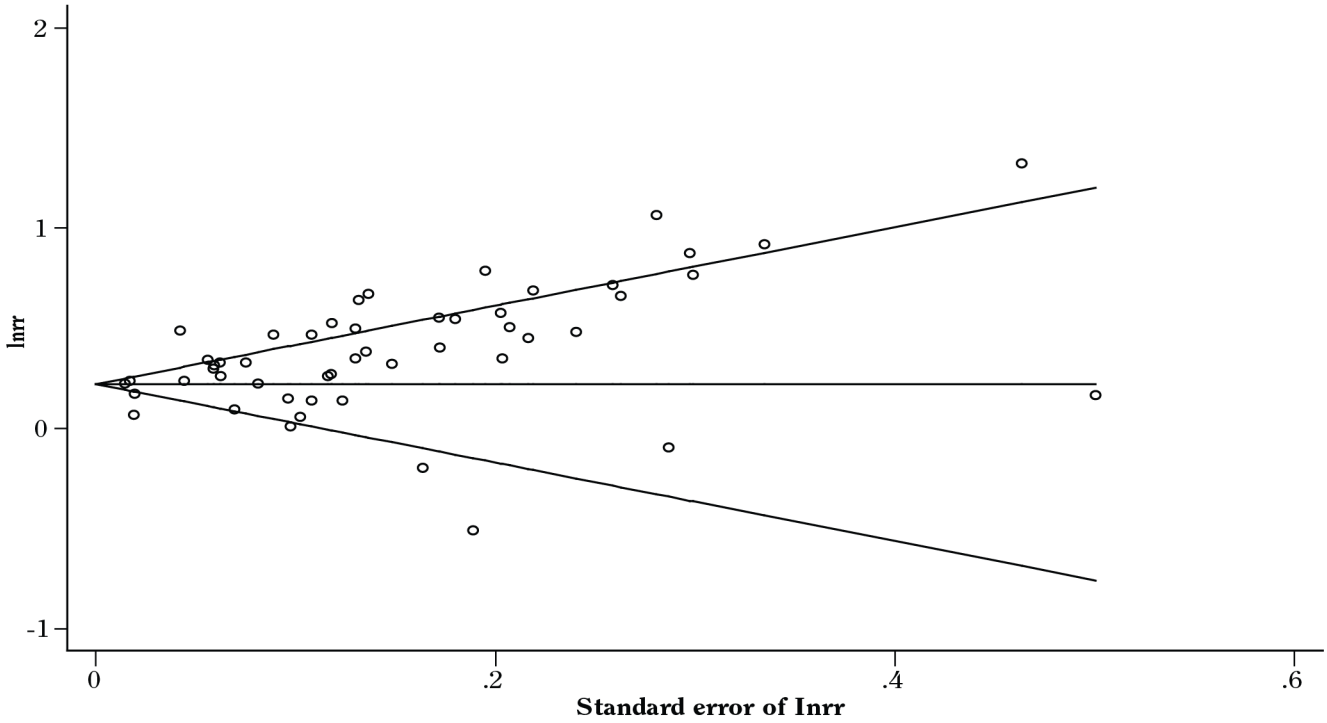
**Figure 10.1 Adjusted relative risk (RR) of diabetes, current smokers compared with nonsmokers**



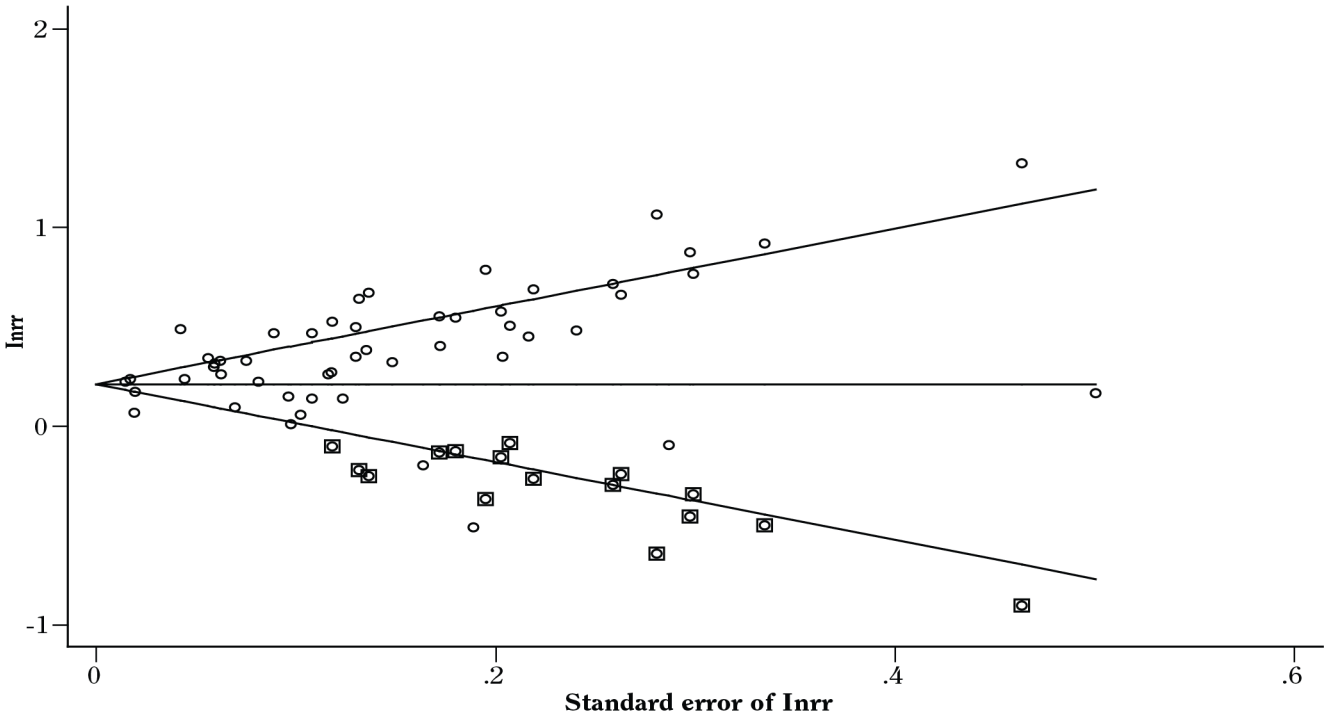

*Note:* **CI** = confidence interval.

**Figure 10.2 Log relative risk of diabetes for current smokers, funnel plots without (A) and with 225 (B) trim-and-fill procedure**

**A. Begg's funnel plot with pseudo 95% confidence limits**




**B. Begg's funnel plot with pseudo 95% confidence limits (using trim-and-fill method)**




*Note:* **lnrr** = natural log of relative risk.

**Table 10.9 Stratified analyses of pooled relative risk (RR) for incident diabetes from smoking**

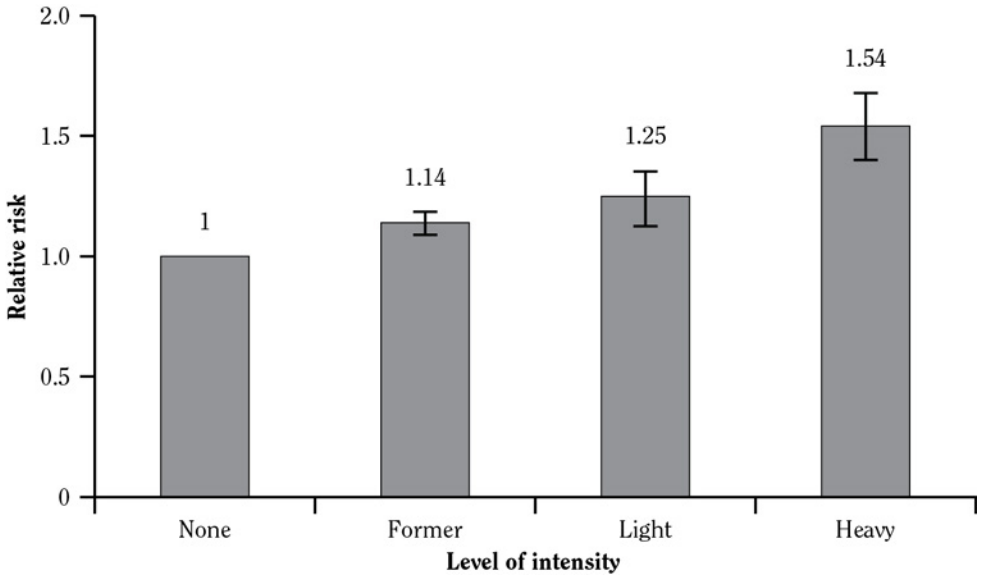
| Stratified analysis | Number of comparisons | Pooled RR (95% CI) | Heterogeneity |
|---|---|---|---|
| Adjustment for confounding factors | | | |
| Minimal (≤3) | 6 | 1.44 (1.08–1.92) | 0.012 |
| Moderate (4–7) | 15 | 1.33 (1.18–1.50) | <0.001 |
| Substantial (≥8) | 30 | 1.39 (1.32–1.47) | <0.001 |
| Type of outcome measure | | | |
| Biologic | 29 | 1.39 (1.29–1.49) | <0.001 |
| Reported by patient or physician | 14 | 1.37 (1.23–1.53) | <0.001 |
| Registry or database | 8 | 1.31 (1.23–1.39) | 0.063 |
| Type of screening at baseline | | | |
| Biologic measures | 29 | 1.39 (1.29–1.51) | <0.001 |
| Reported by patient or physician or database | 22 | 1.35 (1.27–1.44) | <0.001 |
| Fasting glucose threshold (mg/dL) | | | |
| ≥140 | 6 | 1.74 (1.39–2.18) | 0.014 |
| ≥126 or 120 | 22 | 1.42 (1.29–1.57) | <0.001 |
| ≥110 or 100 | 4 | 1.26 (1.04–1.53) | 0.013 |
| Not specified | 19 | 1.32 (1.24–1.41) | <0.001 |
| Mean follow-up (years) | | | |
| ≤10 | 24 | 1.46 (1.33–1.60) | <0.001 |
| >10 | 25 | 1.32 (1.25–1.40) | <0.001 |
| Year of publication | | | |
| Before 2000 | 6 | 1.45 (1.08–1.94) | 0.001 |
| 2000–2005 | 19 | 1.39 (1.27–1.52) | <0.001 |
| 2006–2009 | 26 | 1.36 (1.28–1.43) | <0.001 |
| Smoking intensity/exposure to nicotine | | | |
| Primary predictor | 31 | 1.42 (1.32–1.53) | <0.001 |
| Cofactor for risk | 19 | 1.32 (1.25–1.39) | 0.001 |
| Mean age (years) | | | |
| <50 | 26 | 1.37 (1.29–1.45) | <0.001 |
| ≥50 | 25 | 1.38 (1.28–1.49) | <0.001 |
| Mean BMI | | | |
| <25 | 20 | 1.40 (1.26–1.55) | <0.001 |
| ≥25 | 27 | 1.36 (1.29–1.43) | <0.001 |
| Missing information | 4 | 1.53 (1.16–2.02) | 0.060 |
| Study location | | | |
| America | 10 | 1.38 (1.24–1.55) | <0.001 |
| Europe or Australia | 25 | 1.36 (1.29–1.44) | <0.001 |
| Asia | 16 | 1.41 (1.25–1.59) | <0.001 |
| Gender | | | |
| Male | 24 | 1.41 (1.31–1.52) | <0.001 |
| Female | 12 | 1.26 (1.15–1.38) | <0.001 |
| Both genders | 19 | 1.44 (1.31–1.58) | 0.008 |

**Table 10.9 Continued**

| Stratified analysis | Number of comparisons | Pooled RR (95% CI) | Heterogeneity |
|---|---|---|---|
| Smoking intensity[a] | | | |
| Former smokers vs. never smokers | 33 | 1.14 (1.09–1.19) | 0.033 |
| Light smokers vs. nonsmokers | 22 | 1.25 (1.14–1.37) | <0.001 |
| Heavy smokers vs. nonsmokers | 23 | 1.54 (1.40–1.68) | <0.001 |

*Note:* **BMI** = body mass index (weight in kilograms divided by height in meters squared); **CI** = confidence interval; **mg/dL** = milligrams per deciliter.
[a]Light smoking defined in most studies as current smoking of 0–19 cigarettes/day (0–15 in some studies), and heavy smoking defined in most studies as current smoking of 20 or more cigarettes/day (15 or more in some studies).

**Figure 10.3 Pooled relative risk of diabetes associated with various levels of smoking intensity**




*Note:* Light smoking defined in most studies as current smoking of 0–19 cigarettes/day (0–15 in some studies), and heavy smoking defined in most studies as current smoking of 20 or more cigarettes/day (15 or more in some studies).

## Evidence Synthesis

All studies included in the meta-analysis were of the cohort design and prevalent diabetes cases were excluded at baseline, establishing an unambiguous temporal relationship between smoking and diabetes. Various lines of evidence support biological plausibility. A series of biologic experiments in animals and humans provides convincing evidence that cigarettes and one pharmacologically active component in cigarette smoke, nicotine, are strongly implicated in the development of insulin resistance and irregularities in glucose metabolism.

The association is strong and consistent. The meta-analysis revealed that smoking is associated with a 30–40% increased risk of developing type 2 diabetes, and the results were robust in various stratified analyses. Additionally, the positive association between smoking and diabetes has been replicated in numerous studies in multiple countries. The quantitative summary shows that as the amount of smoking increases (defined by number of cigarettes smoked/day), the RR of diabetes increases in a dose-response manner. Furthermore, the meta-analysis described in this chapter found that former smokers have a lower risk of developing diabetes than current smokers.

Alternative explanations for causation can be set aside. Smoking is associated with other behaviors—such as physical inactivity, poor diet, and high alcohol intake—that favor weight gain and/or diabetes, but most of the

studies in this meta-analysis controlled for such factors. Thus, residual confounding seems unlikely as an explanation for the association of smoking with diabetes. Furthermore, RRs were not attenuated in the studies that carefully adjusted for these confounding factors, indicating that the effects of smoking are independent of other lifestyle factors.

Concerns about specificity of causation do not apply in interpreting this association as smoking is associated with multiple diseases through many different mechanisms and pathways, and multiple factors contribute to the risk of diabetes. Lack of specificity is not a requisite for inference of causality (USDHHS 2004).

## Conclusions

1. The evidence is sufficient to infer that cigarette smoking is a cause of diabetes.

2. The risk of developing diabetes is 30–40% higher for active smokers than nonsmokers.

3. There is a positive dose-response relationship between the number of cigarettes smoked and the risk of developing diabetes.

## Implications

Smoking should be considered an important and modifiable risk factor for the development of diabetes. Given the increasing epidemic of diabetes worldwide and the high prevalence of smoking in most developing countries, reducing tobacco use should be promoted as a key public health strategy to prevent and control the global epidemic of diabetes. Because smoking is also associated with increased risk of cardiovascular disease and death among persons with diabetes (Al-Delaimy et al. 2001, 2002; Spencer et al. 2008), it has enormous implications for diabetes, increasing its incidence and its complications.

# Immune Function and Autoimmune Disease

This section considers the evidence related to the adverse effects of smoking on the immune system and whether smoking is a cause or contributory cofactor in immunologically mediated diseases. This section also covers the current understanding of the cellular and molecular mechanisms by which smoking affects immunity (Holt and Keast 1977; Sopori 2002; Stampfli and Anderson 2009). Previous reports from the Surgeon General have not covered this topic in depth. Several reports have covered effects of smoking on respiratory immunity, most recently in 2010, and diseases for which the immune system plays a key role (Tables 10.10–10.12) (USDHHS 2010).

## Description of the Literature Review

The theme of smoking, immunity, and immunologically mediated diseases covers a wide range of topics and potential search terms. To develop this section, literature databases were searched through March 2012, using a search string strategy that combined the following key search terms:

Smoking OR smoke OR cigarette OR cigarette smoke OR cigarette smoke extract OR tobacco OR tobacco smoke individually with each of the following key descriptors of immunity: immunity, host defense, adaptive, innate, infection, immune disease, autoimmunity, rheumatoid, lupus, multiple sclerosis, HIV/AIDS, virus, influenza, RSV, adenovirus, bacteria, pseudomonas, *Haemophilus,* streptococcus, cancer, adenocarcinoma, NSCLC, small cell lung cancer, immune surveillance, lymphocyte, T cell, B cell, humoral response, antibody, NK cell, NKT cell, dendritic cell, granulocyte, neutrophil, macrophage, monocyte, TAM, tumor associated macrophage, tolerance, central tolerance, peripheral tolerance, innate immunity, PRR, PAMP, DAMP, HMGB1, Toll-like receptor, TLR (collectively and individually for the known TLRs), myeloid differentiation factor 88 (MyD88), RIG, helicase, alarmin, type 1 interferon response, inflammasome, Th1, Th2, Th17, Treg, Breg, CTL, cytotoxic T cell, mononuclear cell, macrophage, M1, M2, eosinophil, neutrophil, dendritic cell, epithelium,

**Table 10.10 Conclusions about the adverse effects of tobacco use and exposure to tobacco smoke on infectious diseases, from previous Surgeon General's reports**

| Selected conclusions | Year and page number of Surgeon General's report |
|---|---|
| 1. The evidence is sufficient to infer a causal relationship between smoking and acute respiratory illnesses, including pneumonia, in persons without underlying smoking-related chronic obstructive lung disease. | 2004, p. 27 |
| 2. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and acute respiratory infections among persons with preexisting chronic obstructive pulmonary disease. | 2004, p. 27 |
| 3. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and lower respiratory illnesses in infants and children. | 2006, p. 14 |
| 4. The increased risk for lower respiratory illnesses is greatest from smoking by the mother. | 2006, p. 14 |

*Source:* U.S. Department of Health and Human Services 2004, 2006.

post-translational modification, carbonylation, acetylation, nitrosylation, unfolded protein stress response, heme oxygenase (HMOX), carbon monoxide, nicotine, acrolein, aryl hydrocarbon receptor, AHR, epigenetic, microRNA, regulatory RNA, HDAC, histone modification.

This search strategy returned more than 5,000 primary references. The subsequent analysis focused on (a) evidence from larger, well-powered studies and major meta-analyses of the clinical and epidemiologic literature and (b) basic science papers published since 1985, which covers a timeframe known for major technical advances in cellular and molecular immunology. However, some relevant smaller scale clinical investigations and some earlier basic science papers have also been considered because of their quality and relevance.

## Overview of Innate and Adaptive Immune Defense

The immune system exerts its beneficial and detrimental effects via a complex, highly cross-regulated network of cellular and molecular defense mechanisms. Therefore, any discussion of the effects of smoking on immunity should consider the multiple and richly interconnected tiers of immunological defenses that include innate defense mechanisms, such as barrier functions, soluble defense molecules, and cellular defenses and adaptive immune responses (Figure 10.4).

Immunity comprises an array of defense mechanisms that protect the host from infection by pathogens (Holt et al. 2008; Kohlmeier and Woodland 2009). Many of these defense mechanisms are mediated by protective inflammation. The immune system also plays a central role in internal homeostasis, guarding against malignant transformation to prevent cancer and responding to tissue damage after injury (Oppenheim and Yang 2005; Rock et al. 2010; Vesely et al. 2011). In health, the immune system does not normally damage host tissue or attack the diverse self-antigens in the human body because of a state of self-tolerance (Wing and Sakaguchi 2010). However, when turned against the host, immune mechanisms can contribute to an array of disorders, many of which have an inflammatory basis and, in extreme cases, provoke autoimmune diseases, such as systemic lupus erythematosus (SLE or lupus).

Conventionally, the immune system is divided into two broad tiers: innate immunity and adaptive immunity. Innate immunity represents a large family of effector mechanisms, including barrier functions, soluble defense molecules that provide nonspecific protection against harmful agents, and cellular defenses triggered by pattern recognition receptors (PRRs) that recognize conserved pathogen-associated molecular patterns (PAMPs) (Table 10.13) (Janeway 1989; Kawai and Akira 2011). Innate immune mechanisms play an important role in responding to tissue damage. These responses arise when so-called damage associated molecular patterns (DAMPs) that are normally cryptic, become exposed after injury and activate immune cells via PRRs (Matzinger 2002; Rock et al.

**Table 10.11 Conclusions about the adverse effects of tobacco use and exposure to tobacco smoke on asthma, from previous Surgeon General's reports**

| Selected conclusions | Year and page number of Surgeon General's report |
|---|---|
| 1. In persons with asthma, the evidence is inadequate to infer the presence or absence of a causal relationship between smoking and acute asthma exacerbation. | 2004, p. 27 |
| 2. The evidence is sufficient to infer a causal relationship between active smoking and respiratory symptoms in children and adolescents, including coughing, phlegm, wheezing, and dyspnea. | 2004, p. 27 |
| 3. The evidence is sufficient to infer a causal relationship between active smoking and asthma-related symptoms (i.e., wheezing) in childhood and adolescence. | 2004, p. 27 |
| 4. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and physician-diagnosed asthma in childhood and adolescence. | 2004, p. 27 |
| 5. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and a poorer prognosis for children and adolescents with asthma. | 2004, p. 27 |
| 6. The evidence is sufficient to infer a causal relationship between active smoking and all major respiratory symptoms among adults, including coughing, phlegm, wheezing, and dyspnea. | 2004, p. 28 |
| 7. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and asthma in adults. | 2004, p. 28 |
| 8. The evidence is sufficient to infer a causal relationship between active smoking and poor asthma control. | 2004, p. 28 |
| 9. The evidence is sufficient to infer a causal relationship between parental smoking and ever having asthma among children of school age. | 2006, p. 14 |
| 10. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and the onset of childhood asthma. | 2006, p. 14 |
| 11. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and adult-onset asthma. | 2006, p. 16 |
| 12. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and a worsening of asthma control. | 2006, p. 16 |
| 13. The evidence is sufficient to conclude that there is a causal relationship between active smoking and wheezing severe enough to be diagnosed as asthma in susceptible child and adolescent populations. | 2012, p. 9 |

*Source:* U.S. Department of Health and Human Services 2004, 2006, 2012.

2010). The term "alarmin" describes collectively an array of structurally diverse host proteins that are released after tissue injury or during infection to mobilize host defense and tissue repair mechanisms. These innate immune mediators include interleukin-1alpha (IL-1α) and related members of the IL-1 family (e.g., IL-18, IL-33), S100 proteins, defensins, heat-shock proteins (HSPs), uric acid, antibacterial peptides, hepatoma-derived growth factor, eosinophil-derived neurotoxin, cathelicidins, nucleotides, interferons (IFNs), and high mobility group box 1 (HMGB1) (Oppenheim and Yang 2005).

The main cell types involved in mediating innate immunity are epithelial cells and leukocytes, especially granulocytes (neutrophils and eosinophils) and mononuclear lineage cells (monocyte and macrophage subpopulations) (Figure 10.5). Macrophages play a critical role in the destruction of pathogens and the removal of cell debris and dying cells (Metschnikoff 1887; Murray and Wynn 2011), but neutrophils and other cell types have important phagocytic activities (Walsh et al. 1999; Soehnlein and Lindbom 2010). Macrophage phagocytosis is usually accompanied by macrophage activation, which

**Table 10.12 Conclusions about the adverse effects of tobacco use and exposure to tobacco smoke on chronic obstructive pulmonary disease, from previous Surgeon General's reports**

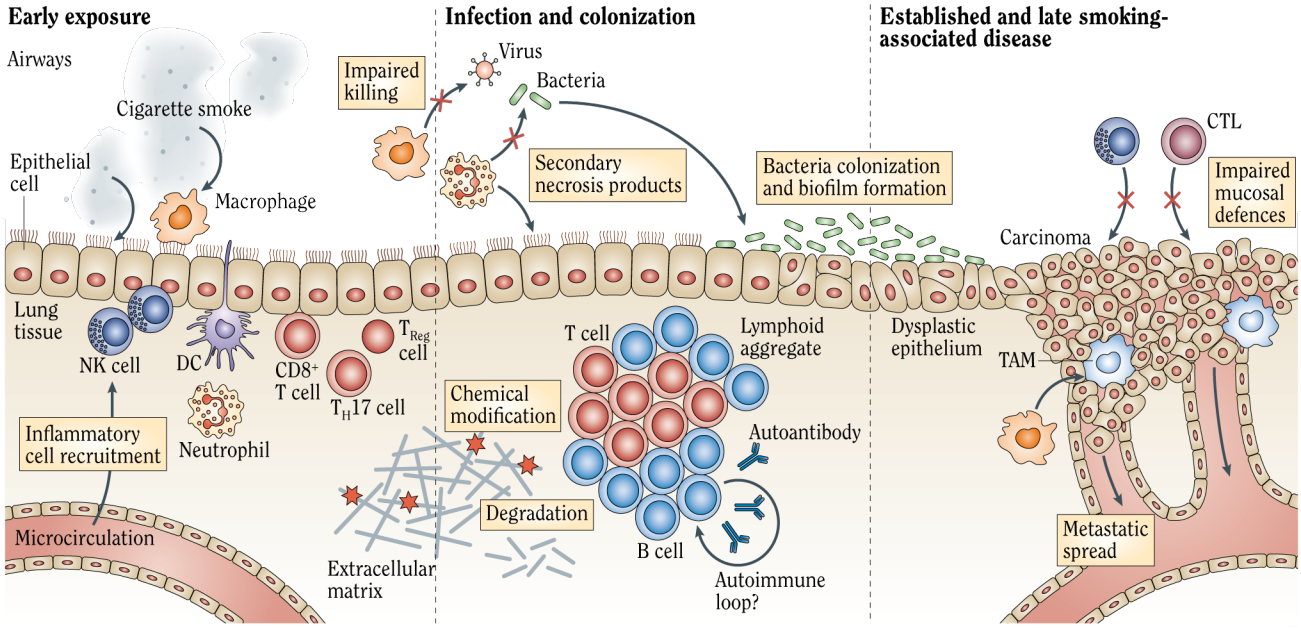
| Selected conclusions | Year and page number of Surgeon General's report |
|---|---|
| 1. Active smoking causes injurious biologic processes (i.e., oxidant stress, inflammation, and a protease-antiprotease imbalance) that result in airway and alveolar injury. This injury, if sustained, ultimately leads to the development of chronic obstructive pulmonary disease. | 2004, p. 27 |
| 2. The evidence is sufficient to infer a causal relationship between active smoking and chronic obstructive pulmonary disease morbidity and mortality. | 2004, p. 28 |
| 3. The evidence is inadequate to infer the presence or absence of a causal relationship between a lower cigarette tar content and reductions in chronic obstructive pulmonary disease-related mortality. | 2004, p. 28 |
| 4. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and risk for chronic obstructive pulmonary disease. | 2006, p. 16 |
| 5. The evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and morbidity in persons with chronic obstructive pulmonary disease. | 2006, p. 16 |
| 6. Oxidative stress from exposure to tobacco smoke has a role in the pathogenetic process leading to chronic obstructive pulmonary disease. | 2010, p. 11 |
| 7. Protease-antiprotease imbalance has a role in the pathogenesis of emphysema. | 2010, p. 11 |
| 8. Inherited genetic variation in genes such as *SERPINA3* is involved in the pathogenesis of tobacco caused chronic obstructive pulmonary disease. | 2010, p. 11 |
| 9. Smoking cessation remains the only proven strategy for reducing the pathogenetic processes leading to chronic obstructive pulmonary disease. | 2010, p. 11 |

*Source:* U.S. Department of Health and Human Services 2004, 2006, 2010.

leads to a proinflammatory and procoagulant state. Other cells—notably natural killer (NK) cells and natural killer T (NKT) cells (Berzins et al. 2011; Sun and Lanier 2011), mast cells (Galli et al. 2005), and nuocytes (Neill et al. 2010), which lack conventional surface markers—constitute important components of innate immunity. Innate reactions characteristically can be activated very rapidly but do not hold a molecular memory of past immunologic exposures.

The main cell types involved in mediating adaptive immunity are T and B lymphocytes (T cells and B cells) (Figure 10.5). In contrast to innate immunity, adaptive immunity retains memory of past insults, such that if an individual encounters the same insults later in life, a much more rapid and amplified response can be mounted. T cells respond mostly to short peptide fragments of foreign proteins (antigens) presented in the context of major histocompatibility complex (MHC) Class I or II (MHC I or II) proteins (Zinkernagel and Doherty 1974). Antigens must usually be presented to T cells by specialized antigen-presenting cells, of which the dendritic cell subtypes are among the most important (Steinman and Cohn 1973; Banchereau and Steinman 1998). Presentation of soluble, mainly extracellular proteins is mediated by MHC II, whereas intracellular proteins (for example from an intracellular pathogen such as a virus) are presented on MHC I molecules. T cells, with the surface marker CD4, classically recognize MHC II, whereas CD8 positive (CD8+) lymphocytes recognize antigen on MHC I molecules. Human self-antigens are also presented on MHC I molecules constitutively but do not trigger immune reactions because of tolerance (i.e., protective processes). T cells exert their effects by differentiating into effector cells able to secrete cytokines and chemokines that regulate defensive inflammation. Some T lymphocytes differentiate into cytotoxic cells that kill cellular targets. B cells recognize unprocessed antigen in its natural configuration and exert their effects largely by producing one of the five major

**Figure 10.4 Overview of immune defects caused by smoking in the lungs**




*Source:* Stampfli and Anderson 2009. Reprinted with permission from Macmillan Publishers Ltd., © 2009.
*Note:* Cigarette smoke has both proinflammatory and immune-suppressive effects on the immune system. Acute effects of smoke on macrophages and epithelial cells promote inflammation by inducing the recruitment of cells from the microcirculation to the lungs. At the same time, cigarette smoke impairs innate defense mechanisms by macrophages, epithelial cells, dendritic cells, and natural killer cells, thereby increasing the risk, severity, and duration of infection. The transition to a more severe expression of smoking-associated disease is marked by the impaired ability of macrophages to kill bacteria or viruses, the loss of ability to remove dead cells, the degradation and chemical modification of the extracellular matrix, the increasing retention of oligoclonally expanded CD8+ T cells and the induction of interleukin-17-secreting effector T cells. After long-term exposure to cigarette smoke, germinal centers with T cells and B-cell zones may form at the site, supporting the production of pathogenic autoantibodies and driving autologous disease. Loss of mucosal defenses can lead to bacterial colonization (as occurs in around 30% of long-term smokers with chronic obstructive pulmonary disease). Concurrently, somatic mutations in the epithelium and alteration of macrophage phenotype promote inflammation and the development of cancer (carcinoma in situ) that has a high chance of metastatic spread. **CD** = cluster of differentiation; **CTL** = cytotoxic lymphocytes; **DC** = dendritic cell; **NK** = natural killer; **TAM** = tumor-associated macrophage.

classes of immunoglobulin (Ig) antibodies. This process requires antigen presentation and help from CD4+ T cells, which are designated as CD4+ T helper (Th) cells.

The division between innate immunity and adaptive immunity is convenient but does not reflect the intimate interaction between the two. For example, stimulation of dendritic cells by PRR not only activates these cells to move to secondary lymphoid organs and present antigen but also shapes the nature of the subsequent immune reaction, as PRR stimulation induces specific costimulatory molecules and immune mediators that control T cell polarization and acquisition of effector function (Macagno et al. 2007).

Both overactivated or inappropriate innate and adaptive immune responses can directly damage the host, which leads to inflammation, tissue damage, and disease (Murray and Wynn 2011; Park et al. 2012). Mechanisms underlying these immune-driven pathologies are complex and may include innate and adaptive processes targeted at environmental agents, as well as autoreactive responses that drive autoimmune diseases. The latter are associated with a breakdown in tolerance. Tolerance is conventionally described as constituting central tolerance, where self-reactive lymphocytes are killed by apoptosis in the thymus, or peripheral tolerance, where potentially self-reactive cells survive but are rendered immunologically nonresponsive (Wing and Sakaguchi 2010; Zanoni and Granucci 2011).

Immune surveillance does more than just detect and eliminate or contain pathogens. The immune system

**Table 10.13 Pathogen-associated molecular patterns and their respective pattern recognition receptors**

| Species | PAMPs | TLR usage | PRRs involved in recognition |
|---|---|---|---|
| **Bacteria, mycobacteria** | LPS | TLR4 | |
| | lipoproteins, LTA, PGN, lipoarabinomannan | TLR2/1, TLR2/6 | NOD1, NOD2, NALP3, NALP1 |
| | flagellin | TLR5 | IPAF, NAIP5 |
| | DNA | TLR9 | AIM2 |
| | RNA | TLR7 | NALP3 |
| **Viruses** | DNA | TLR9 | AIM2, DAI, IFI16 |
| | RNA | TLR3, TLR7, TLR8 | RIG-I, MDA5, NALP3 |
| | structural protein | TLR2, TLR4 | |
| **Fungus** | zymosan, beta-glucan | TLR2, TLR6 | Dectin-1, NALP3 |
| | Mannan | TLR2, TLR4 | |
| | DNA | TLR9 | |
| | RNA | TLR7 | |
| **Parasites** | tGPI-mutin *(Trypanosoma)* | TLR2 | |
| | glycoinositolphospholipids *(Trypanosoma)* | TLR4 | |
| | DNA | TLR9 | |
| | hemozoin *(Plasmodium)* | TLR9 | NALP3 |
| | profilin-like molecule *(Toxoplasma gondii)* | TLR11 | |

*Source:* Kawai and Akira 2011. Reprinted with permission from Elsevier, © 2011.
*Note:* **LPS** = lipopolysaccharide; **PAMP** = pathogen-associated molecular pattern; **PRR** = pattern recognition receptor; **TLR** = Toll-like receptor.

is also very actively involved in maintaining homeostasis and continually surveys tissues to eliminate damaged cells and cells that are undergoing malignant transformation (Vesely et al. 2011).

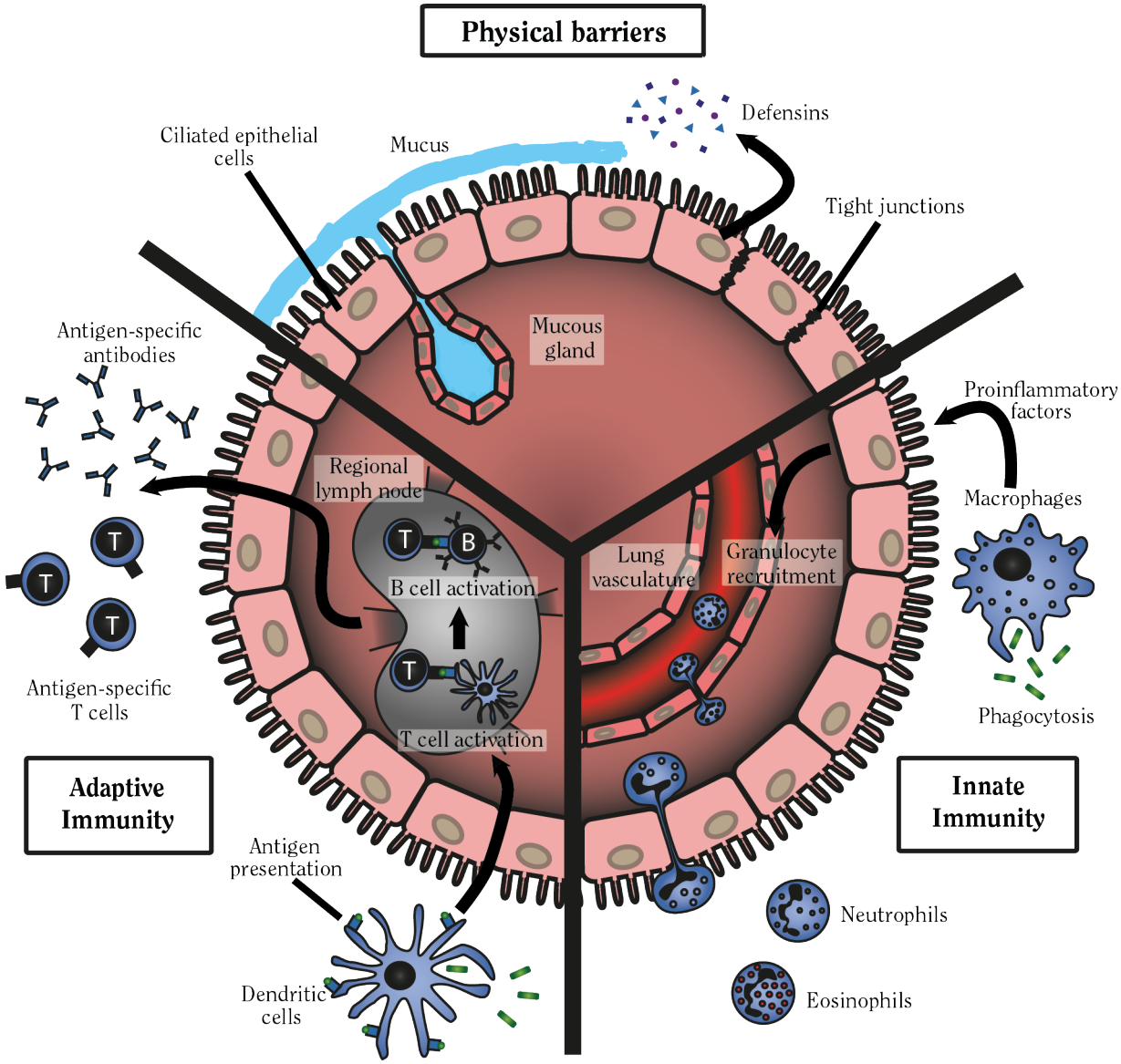
With regard to the effects of cigarette smoking on immunity, a critical issue is the degree to which the marked effects of smoking on inflammation are considered immune effects. Because inflammation is an effector arm of immunity and subserves a defensive role in health, this chapter considers adverse effects of smoking on inflammation, particularly where inflammation is directly part of host defense.

## Nature of Cigarette Smoking in Relation to Immunity

Cigarette smoke is a damaging and proinflammatory complex mixture that can also directly suppress innate and adaptive immune processes (Sopori 2002; Barnes 2004; van der Vaart et al. 2004; Stampfli and Anderson 2009; Vesely et al. 2011), making it a highly unusual insult in the context of immunity.

As reviewed in detail in previous Surgeon General's reports, the gas and particulate phases of cigarette smoke contain more than 7,000 chemical compounds (USDHHS 2004, 2010). These compounds include direct carcinogens (e.g., methylcholanthrene, benzo[*a*]pyrenes [B[*a*]P], and acrolein); toxins (e.g., carbon monoxide [CO], ammonia, acetone, nicotine, and hydroquinone); reactive solids with chemically catalytic surfaces; and oxidants (e.g., superoxide and nitrogen oxides). These components, either individually or in combination, can affect aspects of the immune system. Freshly generated smoke is a reactive mixture abounding in oxidative moieties that are highly chemically reactive (Kodama et al. 1997). Furthermore, smoke condensate can generate secondary oxidative moieties and form multiple types of chemical adducts. These can be formed either directly or secondarily as a consequence of the induction of enzymes, such as nitric oxide synthase, in the host (Rahman et al. 2002). The targets for chemical modification include cell membrane lipids, proteins, intracellular matrix/scaffolds and extracellular matrix, DNA, and organelles. The induced damage can inactivate or perturb the normal function of these critical targets. The modifications can be particularly compromising when they impinge on immune signaling pathways

**Figure 10.5 Diagram of innate and adaptive immunity**




*Source:* Illustration created by Jake Nikota for this Surgeon General's report.
*Note:* To illustrate the various aspects of the immune system, the figure is divided into physical barriers, innate, and adaptive immunity. While this separation is convenient, there is an intimate interaction between innate and adaptive immunity, and individual components never respond in isolation. The ciliated respiratory epithelium forms a physical barrier through tight junctions between individual cells and protects by sweeping particles away in the overlying mucus gel layer. A number of innate defense molecules, including defensins, are found in the epithelial lining fluid. In addition to their barrier function, epithelial cells also have potent innate defense capabilities. The main cell types associated with innate immunity are mononuclear lineage cells (monocyte and macrophage subpopulations) and granulocytes (neutrophils and eosinophils). Macrophages are considered the most important phagocytes, playing a critical role in the destruction of pathogens and the removal of dying cells. Other innate immune cells are natural killer cells, natural killer T cells, mast cells, dendritic cells, and nuocytes. Innate immune responses are activated rapidly but do not hold a molecular memory. T and B lymphocytes (T and B cells) are part of the adaptive immune system. Adaptive immunity retains memory, providing protection against subsequent insult by the same pathogen. T cells respond to short peptide fragments of foreign proteins (antigens) presented by specialized antigen-presenting cells, of which dendritic cells are the most important. Dendritic cells reside within the tissue where they capture antigen. Following activation, dendritic cells migrate to secondary lymphoid organs and present antigen to T cells. Cluster of differentiation (CD)4 T cells exert their effects by differentiating into effector cells that are capable of secreting cytokines and chemokines that regulate inflammation. CD8 T lymphocytes differentiate into cytotoxic cells that kill cellular targets. B cells exert their effect largely by producing antibodies. This process requires antigen presentation and help from CD4+ T cells.

and the extracellular matrix via acetylation, nitrosylation, carbonylation, and oxidation, which can affect cell survival, activation, and differentiation of the effector cells drawn to the sites of smoking-induced damage and inflammation. Furthermore, changes in the conformation of cellular proteins induced by smoking can trigger secondary responses, notably the unfolded protein response (Kelsen et al. 2008).

The diverse and sometimes seemingly contradictory effects of smoking on immunity are best understood by considering that smoking is both an activating and suppressing stimulus (Sopori 2002; Barnes 2004; Stampfli and Anderson 2009); that the components of smoke have different pharmacokinetic distributions to different organs; and that the nature of the effects of smoking vary over time. Smoking exerts its effects systemically, as well as in the lungs. The net effect in any given target organ reflects the intersection of the pharmacodynamics of the disposition of various smoke components and secondarily generated reactive intermediates in the context of individual genetic susceptibility, all of which vary markedly among people and probably over time.

A highly informative pattern has emerged from studies of animals. The pattern is often divided into acute, subchronic, and chronic exposure to smoke, where initially strong effects on acute exposure are compensated subchronically by adaptive processes (e.g., induction of detoxifying and antioxidant enzymes), but in genetically susceptible backgrounds, chronic long-term damage results from attrition and defenses becoming overwhelmed (USDHHS 2010). After smoking cessation following shorter term exposure to smoke, the changes are often reversible, but at critical points, the damage to the immune system can be irreversible.

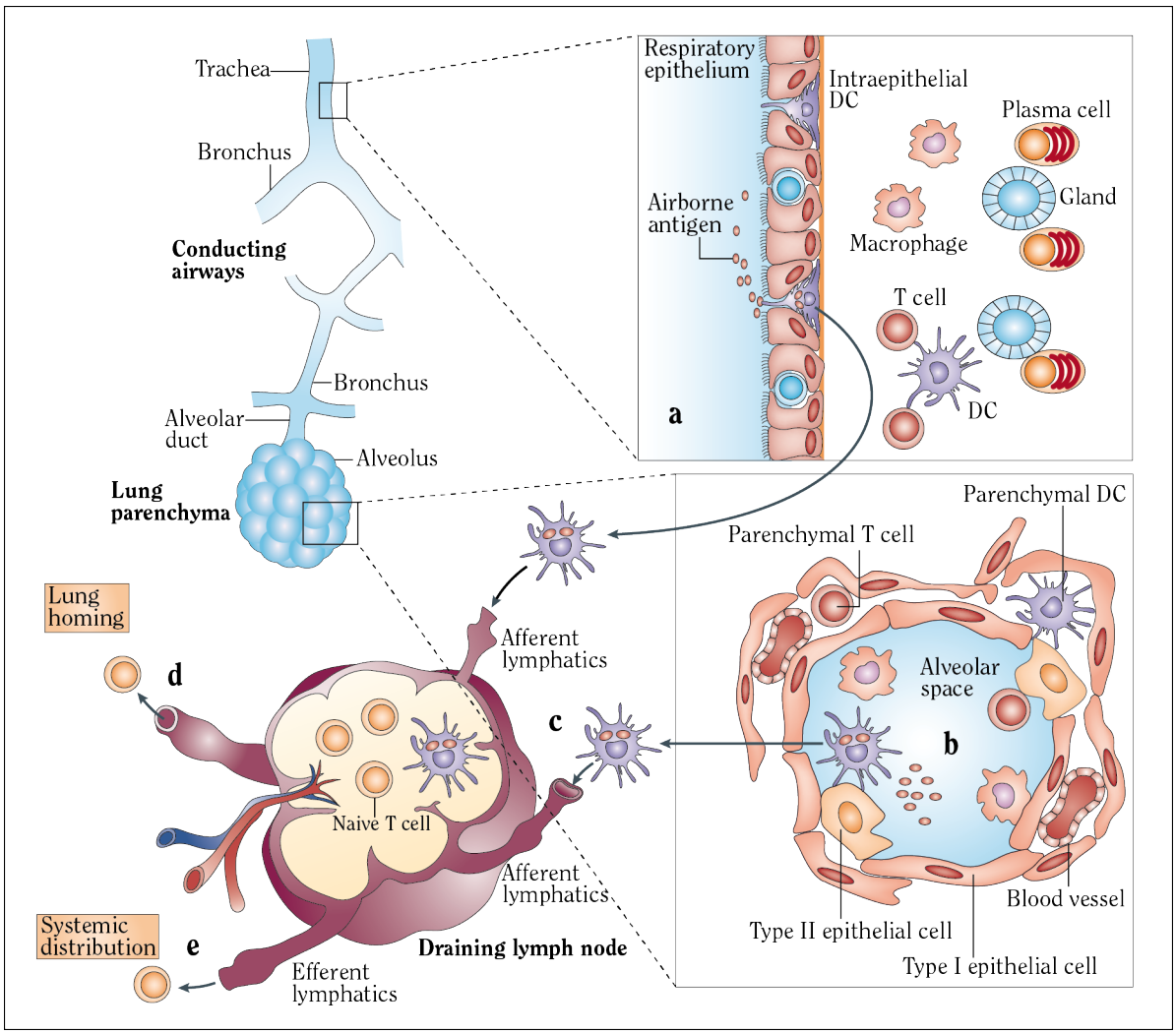
Although tobacco smoke is almost always thought of as a proinflammatory substance, smoking also has suppressive and paradoxical anti-inflammatory effects via its oxidants, CO, nicotine, and some aromatic compounds that modify transcriptional programs (e.g., by activating aryl hydrocarbon receptors [AHRs]). Thus, smoking is able to transiently suppress the key defense process in innate immunity—increasing the likelihood of infection—but later can also promote and amplify inflammation. This property is exemplified by the observation that airway inflammation in people with chronic obstructive pulmonary disease (COPD) who quit smoking increases rather than decreases in the first year after smoking (Willemse et al. 2004). This temporal pattern reflects that active smoking continues to suppress certain defensive inflammatory effector processes in the background of cumulative worsening damage and underlying inflammation. This paradigm of acute-on-chronic cumulative damage is very useful when comparing and understanding the very large experimental dataset on smoking and immunity.

## Adverse Effects of Cigarette Smoke on Specific Cellular and Molecular Mechanisms

There is convincing evidence that cigarette smoke impacts a wide range of host defense functions (Sopori 2002; Barnes 2004; van der Vaart et al. 2004; Stampfli and Anderson 2009; Vesely et al. 2011). Some findings across studies have been inconsistent and controversial. These inconsistencies are likely caused in part by differences in key characteristics of study participants, such as smoking history, genetic susceptibility, and SES. Similar methodological issues can apply to animal models and in vitro systems, in which smoke exposure parameters, such as frequency, duration, and mode of smoke exposure (nose-only versus whole body exposure; sidestream smoke included or excluded) vary greatly among studies. Additionally, experimental systems do not fully represent the circumstance of human smoking, but the results are informative on particular elements of immune response and mechanisms.

The following discussion addresses the effects of cigarette smoke on individual components of the immune system, starting with how inhaled cigarette smoke impacts the respiratory epithelium, as these are the first cells to be exposed to cigarette smoke, followed by more classical innate immune cells, including mononuclear cells and macrophages, and finally adaptive immune cells. The cellular and molecular mechanisms discussed in this section are often studied in isolation in experimental investigations. However, the effects of smoking mediated through these mechanisms occur in the context of the full immune system, and every effect observed in an experimental system, even if statistically significant, may not affect overall immunity. As discussed above, the immune system exerts its effects via a complex, highly cross-regulated and often redundant network of cellular and molecular defense mechanisms. Therefore, moving from observations related to the effect of smoking on a particular element of the immune system to a broader interpretation can be problematic.

**Figure 10.6 The respiratory epithelium**




*Source:* Holt et al. 2008. Reprinted with permission from Macmillan Publishers Ltd., on behalf of Cancer Research UK, © 2008.
*Note:* Local immune cells in the two lung compartments showing capture of airborne antigens and subsequent recognition by T cells in the draining lymph nodes. Luminal antigens are sampled by dendritic cells that are located within the surface epithelium of the bronchial mucosa **(a)** or in the alveoli **(b)**. Antigen-bearing dendritic cells upregulate CC-chemokine receptor 7 and migrate through the afferent lymphatics to the draining lymph nodes and present antigenic peptides to naïve antigen-specific T cells **(c)**. Activated T cells proliferate and migrate through the efferent lymphatics and into the blood via the thoracic duct. Depending on their tissue-homing receptor profile, effector T cells will exit into the bronchial mucosa through postcapillary venules in the lamina propria or through the pulmonary capillaries in the lung parenchyma **(d)**, or disseminate from the bloodstream throughout the peripheral immune system (e.g., to other mucosal sites) **(e)**. **DC** = dendritic cell.

## Respiratory Epithelium

Tobacco smoke reaches the respiratory epithelium at very high concentrations, so that many of the defined effects of smoking on immune effector pathways are exerted on this tissue (Figure 10.6). Far more than a simple barrier, epithelial cells are able to sense microbial agents through PRRs and exert direct antimicrobial effector function (Gribar et al. 2008). This innate immune recognition enables epithelial cells to respond to antigens and allergens, thereby initiating the first step in the host-pathogen interaction, triggering early host defense, and priming the adaptive immune response concurrently. Depending on the level of the airway, the airway epithelium is comprised of a variety of ciliate cells (not found below the bronchi) and secretory cells. This pattern is held in fixed ratio in health, but may change toward more secretory cells, particularly mucus secreting goblet cells as a result of infection. Similarly, the secreted mucins vary in rheology and composition in response to insults. Intercalated between and below the epithelial cells, per se, are antigen-presenting cells (e.g., dendritic cells) and several intraepithelial leukocytes (Lambrecht et al. 1998). The fluid that bathes the epithelium contains an abundance of antioxidants, antiproteases, and innate defense molecules (Widdicombe 1995). Cigarette smoke diminishes key antibacterial defense proteins within the airway lining fluid, including surfactant proteins, beta-defensins, secretory leucocyte protease inhibitors, and lysozymes (Shibata et al. 2008). The epithelium is also metabolically active and able to transform a range of xenobiotics in tobacco smoke. These enzyme systems are induced by cigarette smoke (Spira et al. 2004) and detoxify pollutants but can also convert some carcinogens to more active forms as reviewed in the 2010 Surgeon General's report.

The ciliated respiratory epithelium is a critical defensive barrier able to protect the host against harmful environmental agents. The epithelium forms a barrier via tight junctions between cells and protects by sweeping particles away in the overlying mucus gel layer. Cigarette smoke disrupts the tight bonds at the adherent junctions between epithelial cells, compromising the integrity of the physical epithelial barrier and leading to increased alveolar epithelial permeability (Boucher et al. 1980; Jones et al. 1980). This increased permeability of the respiratory epithelium exposes the lung tissue to inhaled substances, such as microbial agents and other environmental factors. Cigarette smoke further exerts a rapid and adverse effect on mucociliary clearance (Jones et al. 1980; Burns et al. 1989; Dye and Adler 1994).

In vitro studies have demonstrated that cigarette smoke extract activates epithelial cells to produce proinflammatory mediators such as IL-8 (Mio et al. 1997). Contrasting with these observations, cigarette smoke extract attenuates in vitro production of proinflammatory mediators by epithelial cells following stimulation with PAMPs, such as the Toll-like receptor 4 (TLR4) ligand lipopolysaccharide (LPS) (Laan et al. 2004). Cigarette smoke extract also suppresses type I IFN-mediated antiviral immunity following stimulation with double-stranded RNA, a mimic of viral replication, and rhinovirus in lung fibroblast and epithelial cells (Bauer et al. 2008a; Eddleston et al. 2011). In agreement with this observation, influenza-infected nasal epithelial cells from smokers produced less type I IFN than similarly infected nasal epithelial cells from nonsmokers (Jaspers et al. 2010). Moreover, in vitro exposure to cigarette smoke extract modulated rhinovirus-induced chemokine production by airway epithelial cells. Although the neutrophil chemoattractant IL-8 increased in response to rhinovirus infection, expression of chemokine (C-X-C motif) ligand 10 (CXCL-10)—also known as IP-10— and chemokine (C-C motif) ligand 5 (CCL5) was attenuated by cigarette smoke extracts (Eddleston et al. 2011).

Recent evidence from animal models suggests that smoke-exposed epithelium upregulates retinoic acid early transcript 1, the ligand for NK group 2D (NKG2D), rendering it susceptible to NKG2D-mediated cytotoxicity (Borchers et al. 2009). These results imply that aberrant NKG2D ligand expression in the pulmonary epithelium may contribute to the development of structural changes found in COPD and emphysema.

In summary, there is evidence that cigarette smoke activates the airway epithelium to produce proinflammatory mediators, but suppresses the response of the epithelium to viral and bacterial PAMPs. The majority of reports published to-date utilized in vitro exposure of epithelial cell lines or primary cells to cigarette smoke extract. Studies are required to validate these observations in smokers. There is further evidence that smoking compromises airway epithelial host defense by altering the lining fluid, usually by chemical or oxidative inactivation; paralyzing ciliary beating; and damaging the tight junctions between airway epithelial cells.

## Alveolar Macrophages and Mononuclear Cells

Alveolar macrophages play a key role in sensing and eliminating hazardous agents due to their strategic positioning in the luminal space of the lung (Twigg 2004; Murray and Wynn 2011). In health, macrophages protect the host because of their ability to recognize, phagocytose, and destroy pathogens; clear cellular debris before triggering secondary inflammation; and release proresolution and healing growth factors. However, in disease, the destructive capacity of macrophages may damage host tissue,

their failure to clear debris may perpetuate inflammation, and their adoption of certain phenotypes may promote tissue scarring and also exert strong immune suppression on lymphocytes. Partly for these reasons, alveolar macrophages have been discussed as central orchestrators of COPD (Barnes 2004).

Cigarette smoking increases the number of macrophages in the alveolar space of smokers and patients with COPD and activates macrophages to produce proinflammatory mediators, reactive oxygen species, and proteolytic enzymes (Hoidal and Niewoehner 1982; de Boer et al. 2000; Russell et al. 2002), providing a cellular mechanism that links smoking with inflammation and tissue damage. Moreover, cigarette smoking compromises the ability of alveolar macrophages to phagocytose bacteria and apoptotic cells (King et al. 1988; Berenson et al. 2006; Hodge et al. 2007, 2008). The process of removing moribund cells in a sterile manner before they proceed to full necrosis and rupture is called efferocytosis (Vandiver et al. 2006). With regard to COPD, a disease with a high number of apoptotic cells in the lungs, it is tempting to speculate that failure to clear dead cells may lead to secondary inflammation through the release of a number of DAMPs or alarmins, including HMGB1, adenosine triphosphate, HSPs, and IL-1α. Moreover, failure to engage anti-inflammatory and quiescence mechanisms that are usually activated during normal efferocytosis may further perpetuate cigarette smoke-induced inflammation (Liu et al. 2008a). Although of interest, further investigation is required to establish the relevance of these processes to cigarette smoke-induced inflammation and, importantly, human health.

As for the epithelium, smoke impairs PAMP sensing and signaling in humans and mice (Soliman and Twigg 1992; Drannik et al. 2004; Chen et al. 2007b; Gaschler et al. 2008). In a study by Gaschler and colleagues (2009), macrophages isolated from cigarette smoke-exposed mice expressed a skewed inflammatory mediators profile after stimulation with nontypeable *Haemophilus influenza* (NTHi), which caused attenuated levels of TNF-α. In parallel, levels of CCL2, CXCL10, and CCL9 increased significantly.

Nuclear factor-kappa B (NF-κB) is a key inflammatory and regulatory transcription factor. Smoking impairs NF-κB pathway activation in macrophages in response to innate immune stimuli—such as LPS from Gram-negative bacteria, the prototypical agonist of TLR4 (Laan et al. 2004; Birrell et al. 2008). This effect is dependent on oxidative stress, which promotes chemical modification of transduction intermediates in the TLR4/MyD88 pathway by carbonylation (Bozinovski et al. 2011).

Functional phenotyping and gene profiling studies support the division of macrophages into two polarized subsets (Biswas and Mantovani 2010). Mirroring the CD4 Th1/Th2 cell paradigm (Mosmann et al. 1986), macrophages have been divided into the classically activated M1 phenotype at one extreme and the alternatively activated M2 phenotype at the other. M1 and M2 polarization relates to broad transcriptional profiles induced by different activation signals, giving rise to macrophage populations with markedly different properties. M1 cells are classically induced by IFN-γ and are primed for TNF-α production and protease release. M2 polarization is associated with induction of acidic mammalian chitinase and is classically induced in response to helminthic parasites (Mantovani et al. 2005). The balance and intensity of this skewing has direct implications for immunity and disease because effective host defense requires a pathogen-appropriate macrophage activation program. At the level of macrophages, smoking alters the transcriptional profile of effector cells generating an intermediate phenotype. Smoking seems to favor neither of these subsets. Instead, smoking skews the inflammatory mediator profile while suppressing key effector functions, creating a distinctive activation state that distinguishes smokers from nonsmokers (Woodruff 2005; Shaykhiev et al. 2009). This state has been described as "partial M1 deactivation/partial M2 activation" of macrophages. As this skewing is at least partially reversible by reduced glutathione, it is dependent on oxidative damage of effector pathways, but the precise molecular pathways have not been elucidated. This skewing of polarity diminishes the effectiveness of macrophages as agents of host defense, promotes secondary inflammation with attendant proteolytic tissue destruction linked to emphysema, and promotes a profibrotic program related to fixed small airway airflow limitation. Moreover, mononuclear lineage cells are essential for tumor induction, growth, and metastasis under a wide variety of conditions (Condeelis and Pollard 2006). Therefore, smoking induces a partial M2-like state, as this phenotype is most closely associated with cancer. Established tumors have a large volume fraction of macrophages that adopt a strongly immunosuppressive state (tumor-associated macrophages) that prevents immune destruction of tumors. However, while smoking can induce M2-like gene programming, smoke-skewed macrophages are more likely to be polarized further in the direct tumor microenvironment.

In summary, there is clear evidence that exposure to cigarette smoke is associated with an increase in macrophages in the alveolar space in humans, as well as in experimental animals. Although cigarette smoke activates these macrophages to produce proinflammatory and tissue-damaging mediators, smoke paradoxically compromises the ability of alveolar macrophages to sense and phagocytose microbial agents and apoptotic cells.

### NK and NKT Cells

NK cells are generally considered innate immune cells that play a critical role in host defense against microbial agents and tumors (Sun and Lanier 2011). Unlike T and B cells, NK cells do not express antigen-specific receptors that are generated through VDJ (variable, diversity, and joining gene segments) recombination (Murphy 2012). NK cells exert their effector function through direct cell cytotoxicity via the release of perforin and granzymes, Fas cell surface death receptor ligand-induced apoptosis, and proinflammatory cytokine and chemokine release (Hamerman et al. 2005; Swann et al. 2007). Defects in NK function in smokers were first observed in the 1970s (Ferson et al. 1979) and have been replicated since that time (Tollerud et al. 1989; Lu et al. 2006; Mian et al. 2008). The suppressive effect of smoke exposure on NK cell function and number persists after smoking cessation (Hersey et al. 1983).

NKT cells are a small population of thymus-derived T cells expressing an alpha-beta T cell receptor (TCR) (Berzins et al. 2011). Unlike conventional T cells, NKT cells recognize lipid antigens presented on cluster of differentiation (CD1), a small family of nonclassical MHC I-like proteins. NKT cells are viewed as regulatory lymphocytes that play an important role in promoting immunity to tumors, and microbial agents, and suppressing cell-mediated autoimmunity. Kim and colleagues (2008a) described a novel role of CD1-restricted NKT cell-dependent macrophage activation in the development of prolonged inflammatory changes after viral lung infection. However, the study did not address the impact of cigarette smoke on NKT cells after viral infection. Additionally, Vijayanand and colleagues (2007) observed only low numbers of NKT cells in airway biopsies, bronchoalveolar lavage, and induced sputum of subjects with COPD and healthy control subjects; no significant differences were observed between the two groups, an observation consequently confirmed by others.

In summary, evidence suggests that cigarette smoke suppresses NK cell function in humans, as well as in experimental models. In contrast, the effect of smoking on the NKT cell is understudied and clear conclusions cannot be drawn from the current literature.

### Dendritic Cells

Lung dendritic cells are highly efficient antigen-presenting cells. Dendritic cells are indispensable to the initiation of T cell immunity (Mellman and Steinman 2001) and, via a range of PRRs, are an effective component of innate immune defense. Anatomically, dendritic cells are highly susceptible to the effects of smoking because they are usually located subjacent to the respiratory epithelium, although their cellular processes and some cells are also found in the airspace (Figure 10.6) (Jahnsen et al. 2006). Although they are highly efficient in mediating T cell activation, dendritic cells in lung tissue are normally quiescent and only trigger immune reactions after migrating to the T cell area of lymph nodes and upregulating co-stimulatory molecules. However, in diseased tissue, dendritic cells may become competent to activate T cells locally. As with other immune cells, subpopulations with distinct functions are known, and dendritic cells in the lung are often divided into myeloid and plasmacytoid dendritic cells (Tsoumakidou et al. 2008).

Dendritic cell-directed chemokine CCL20 is upregulated in the airways of people with COPD (Demedts et al. 2007), and functional studies in mice have shown that this chemokine contributes to the infiltration of dendritic cells after exposure to cigarette smoke (Bracke et al. 2006). Functionally, increased numbers of dendritic cells likely contribute to the adjuvant properties of cigarette smoke, in part through granulocyte macrophage colony-stimulating factor (GM-CSF)-dependent mechanisms (Trimble et al. 2008). Further evidence suggests that myeloid dendritic cells in the lung promote Th1 and Th17 responses in human emphysema (Shan et al. 2009), linking dendritic cells with disease progression in COPD. However, other evidence indicates that exposure to cigarette smoke decreases the number of dendritic cells in mice (Robbins et al. 2004, 2008). Functional studies suggest that exposure to cigarette smoke decreases the expression of costimulatory molecules and the Th1 cell-inducing cytokine IL-12 and IL-23 by dendritic cells, at least in smoke exposure models involving mice (Robbins et al. 2004, 2008; Kroening et al. 2008). These effects have been linked to immune skewing, predisposing to asthma (Vassallo et al. 2005).

A limited number of studies have investigated the effect of cigarette smoking on dendritic cells in the lungs of healthy smokers and people with COPD. As discussed by Tsoumakidou and colleagues (2008), different and seemingly conflicting results have been reported on the number and function of dendritic cells in COPD. For example, clinical studies show that smokers have a reduced number of dendritic cells in large airways (Rogers et al. 2008) and an increased number, with an immature phenotype, in small airways (Demedts et al. 2007). Complicating the interpretation of the clinical data further is the observation that the number of dendritic cells may expand and contract very rapidly, particularly in response to steroid treatments (Brokaw et al. 1998). In nonhuman primates, the Th1 cell-suppressing and Th2 cell-inducing activity of smoke was most pronounced when exposure

commenced in utero (Wang et al. 2008b). In vitro, cigarette smoke extract augmented the production of IL-8 and suppressed the release of TNF-α, *IL-6*, and IFN-α by plasmacytoid dendritic cells. This effect appeared to be mediated via suppression of PI3K/Akt signaling in plasmacytoid dendritic cells (Mortaz et al. 2009). Mechanistically, both oxidative stress and nicotine have been associated with induction of a proinflammatory dendritic cell state (Vassallo et al. 2008).

In summary, dendritic cells play an important role in the initiation and perpetuation of innate and adaptive immune responses. The effect of cigarette smoke on dendritic cells is mixed. Some evidence indicates that the number of dendritic cells increases in response to exposure to cigarette smoke in humans and mice, although other reports are contradictory. Clinically, these differences may relate to the site that was studied, as smoke may affect dendritic cells differentially in the large and small airways. Data may also be influenced by current treatment with anti-inflammatory agents that are known to affect dendritic cells. Differences observed in animal studies may result from differences between exposure protocols.

### Mast Cells

Mast cells are innate immune sentinel cells that reside in proximity to epithelia, blood vessels, nerves, smooth muscle cells, and mucus-producing glands (Galli et al. 2005). Upon activation, mast cells release a range of different bioactive molecules, including histamine. Research has long shown that mast cells are involved in defense against parasites and closely associated with allergic disorders, playing a critical role in type 1 hypersensitivity reactions (Bischoff 2007). Although evidence reveals that smokers have higher numbers of mast cells in their sputum compared with former smokers (Wen et al. 2010), the impact of cigarette smoke on the function of mast cells and their role in the pathogenesis of smoking-related disorders is poorly understood (Mortaz et al. 2011). In people with COPD, mast cell populations are associated with phenotype and severity (Andersson et al. 2010; Ballarin et al. 2012).

### Nuocytes

Nuocytes are a novel lineage of immune effector cell and are distinguished by their lack of conventional surface markers (Neill et al. 2010). Nuocytes represent an innate effector cell that appears to play a critical role in type 2 immune responses. The effect of smoking on these cells is not known.

### T Cells

T cells are centrally important immune initiators, regulators, and effectors (Castellino and Germain 2006; Zhu et al. 2010). CD4+ Th cells recognize processed extracellular antigen presented in the context of MHC II molecules and differentiate into armed effectors that are able to mediate effects via distinct cytokine secretion patterns. Mosman and colleagues (1986) were the first to describe Th1 cells and Th2 cells as two functional subsets of CD4+ T cells. This division is based on cytokine production: Th1 cells produce IL-2, IFN-γ, and GM-CSF; and Th2 cells produce IL-3, IL-4, IL-5, and IL-13 (Mosmann 1992). Th1 cell-polarized responses are associated with delayed type hypersensitivities, macrophage activation, and immunoglobulin G (IgG) responses. Th2 cell-polarized responses are linked to atopy, allergy, and immunoglobulin (IgE) production. While mechanisms that control Th1 cell- and Th2 cell-polarization are well-understood, research is expanding into other CD4+ T cell subsets, including Th9 and Th17, as well as regulatory T cells and T follicular helper cells (Zhu et al. 2010). CD8+ T cells respond to intracellular antigens presented on MHC I molecules and develop into cytokine-secreting and cytotoxic effectors. Because TCR binding to antigen is highly specific and few primary cells are matched to a given antigen, expansion of responsive clones is a central process in immunity. After expansion and execution of their effector function, the majority of T cells die by apoptosis, leaving only a small residual number of antigen-experienced memory cells.

Cigarette smoke has strong and direct effects on the gene expression profile of the T cell (Charlesworth et al. 2010). Evidence suggests that smoke affects T cell polarity—that is, the net pattern of cytokines and surface stimulator molecules expressed that in turn defines function. Studies have described effector populations within CD4+ Th1 (IFN-γ high) cells and Th17 (IL-17 high) cells (Barceló et al. 2008; Harrison et al. 2008; Chen et al. 2011; Shan et al. 2012). Although the concept of Th1 and Th17 or other subtypes of lymphocytes (and macrophages) is convenient, cytokine expression in effector populations is a stochastic process and polarization signifies a change in the statistical probability distribution profile of gene expression in populations of cells rather than the creation of distinct cellular entities. While oligoclonal expansion of CD4+ cells is documented in humans (Korn et al. 2005; Sullivan et al. 2005), the specificity of these T cells is not well-understood but is important nonetheless, because these cells may be directed against self-antigens, indicative of autoimmune processes, or environmental agents (e.g., viruses and bacteria) that may help to explain the

relationship between viral infection and emphysema in experimental models (Kang et al. 2008).

The retention of CD8+ T cells in the lungs of chronic smokers warrants particular attention, as it is a hallmark of COPD (O'Shaughnessy et al. 1997; Saetta et al. 1999). CD8+ T cells can kill cells through T cell-mediated cytotoxicity (Kagi et al. 1996), and these cells can activate alveolar macrophages to produce MMP-12 (Grumelli et al. 2004). MMP-12 is a potent elastin-degrading enzyme that has been linked to emphysema (Hautamaki et al. 1997). Evidence in mice exposed to cigarette smoke suggests that CD8+ T cells are required for inflammation and emphysematous destruction (Maeno et al. 2007). In mice that were chronically exposed to cigarette smoke, CD8+ T cells were oligoclonally expanded and persisted following cessation of smoke exposure (Motz et al. 2008). TCR analysis by polymerase chain reaction amplification followed by spectratyping showed preferential expansion of CD8+ T cells using Vβ7, Vβ9, and Vβ13. Similar oligoclonal expansion was observed in the lungs of smokers and persons with emphysema (Korn et al. 2005; Sullivan et al. 2005).

At present, the mechanisms responsible for this oligoclonal T cell expansion in animal models and human smokers remain unknown. It is not known whether specific antigens drive oligoclonal T cell expansions or, alternatively, whether cigarette smoke directly promotes a reduction in the breadth of the TCR repertoire. Speculatively, the decline in TCR repertoire may contribute to the increased viral infection susceptibility observed in smokers (USDHHS 2004).

Functional studies by Kalra and colleagues (2000) found that exposure to cigarette smoke induced a state of T cell anergy in rats via depletion of intracellular calcium ions. This observation critically contributes to the notion that cigarette smoke is an immunosuppressive agent (Sopori 2002). Subsequent studies in mice and humans did not confirm these observations (Zavitz et al. 2008). The impact of cigarette smoke on T cell responsiveness may be dose-dependent, as serum cotinine levels were markedly different between the two studies. Furthermore, TCR signaling may not be affected at moderate doses of cigarette smoke, and effects on innate immune cells—such as epithelial cells, macrophages, and NK cells—may predominate.

In summary, there is conclusive evidence that both CD4+ and CD8+ T cells accumulate in the lungs of smokers and persons with COPD. Although the evidence suggests that smoking has direct effects on the gene expression profiles of T cells and skews the T cell polarity toward Th1/Th17, major gaps remain in our understanding of cigarette smoke's effect on T cells. Little is known about the specificity and function of T cells accumulating in the lungs following exposure to cigarette smoke. Moreover, the mechanisms that contribute to T cell accumulation and their role in processes that contribute to the pathogenesis of smoking-related diseases remain poorly understood.

### B Cells and Antibody-Mediated Autoimmunity

B cells are classically viewed as the cells that form antibodies (via plasma cells), but increasing evidence shows that B cells also regulate other immune effects through their ability to secrete cytokines (Harris et al. 2000; Lund and Randall 2010). Although dendritic cells are usually considered the main antigen-presenting cells, stimulated B cells are also highly effective antigen-presenting cells.

B cells are abundant in lungs of people with COPD, and in those of mice that have been chronically exposed to cigarette smoke (Hogg et al. 2004; Gosman et al. 2006; van der Strate et al. 2006). Immunologically, the formation of bronchial-associated lymphoid tissue is of particular interest, because it represents a tertiary lymphoid tissue. Bronchial-associated lymphoid tissue is a hallmark of Stages 3 and 4 of the COPD Global Initiative for Obstructive Lung Disease (Hogg et al. 2004). Similar structures are observed in mice following prolonged exposure to smoke, which provides an opportunity to study the immunologic structure of this function (van der Strate et al. 2006). At present, the role of bronchial-associated lymphoid tissue in the expression and progression of smoking-related diseases is not well-understood. It is also unclear whether the formation of bronchial-associated lymphoid tissue is a direct consequence of exposure to cigarette smoke or secondary to bacterial colonization of the lower respiratory tract.

Cigarette smoking decreases serum levels of all Ig classes, except for IgE (Holt 1987; Edwards 2009). Likewise, animal studies demonstrated that antibody responses to various antigens were reduced significantly as a consequence of chronic exposure to cigarette smoke. Mechanistically, cigarette smoke-exposed macrophages suppress B cell proliferation by producing secondary reactive oxidative metabolites (Hogg et al. 2004; Ishida et al. 2009).

A body of evidence asserts that COPD may be associated with pathogenic autoantibodies (Cosio et al. 2009). To date, three studies have described three autoimmune autoantibody responses: anti-elastin autoimmunity in smokers with emphysema (Lee et al. 2007b), autoantibodies to epithelium in COPD patients (Feghali-Bostwick et al. 2008), and induction of autoimmune emphysema by anti-endothelial antibodies in rats (Taraseviciene-Stewart et al. 2005). Mechanistically, evidence indicates that ciga-

rette smoke serves as an adjuvant (Trimble et al. 2008), possibly because it is a potent inducer of GM-CSF production in the lungs. The role of these autoantibodies in the pathogenesis of COPD remains disputed, because autoantibodies are common in many inflammatory conditions but they may not be pathogenic. Little evidence exists on the systemic effects, despite the fact that proposed smoking-associated autoantigens, such as elastin, are ubiquitous. It is also unclear whether B cell follicles that form in the lungs of long-term smokers are the site of these autoantibody responses.

An emerging body of literature shows that B cell subsets modulate immune responses in an antibody-independent manner by producing cytokines that direct the T cell function (Lund and Randall 2010). Mirroring the Th1/Th2 cell paradigm, B cells have been termed B effector-1 cells and B effector-2 cells based on their cytokine expression profile (Harris et al. 2000). A third subtype of B regulatory cells (Breg or B10) has also been described that produces IL-10 (Yanaba et al. 2009). The effect of cigarette smoke on these B cell subtypes has not been studied.

In summary, there is clear evidence that the number of B cells is increased in people with COPD and in experimental animals after long-term exposure to cigarette smoke. Further evidence suggests that smoking decreases most Ig classes, except for IgE. Emerging literature posits that chronic smoke exposure is associated with the presence of autoantibodies against elastin, as well as the epithelium and the endothelium. However, more experimentation is required to investigate their contribution in perpetuating smoke-induced inflammation and in the pathogenesis of COPD.

## Evidence Synthesis

There is clear evidence that cigarette smoking affects innate and adaptive immunity. Smoking compromises the integrity of the respiratory epithelium and diminishes antibacterial defense proteins in the airway lumen. Smoking is associated with an increase in alveolar macrophages and affects their ability to sense microbial agents and phagocytose bacteria and apoptotic cells. Although some evidence indicates that the number of dendritic cells increases in response to exposure to cigarette smoke in humans and mice, other reports contradict these findings. Cigarette smoking is also associated with increased numbers of T and B cells in the lungs of smokers and people with COPD. Currently, there is only limited information on the function of these cells, as their antigen-specificity and effector function are not well-understood.

## Summary

Two conclusions can be drawn from the current knowledge about the impact of cigarette smoke on the immune system. First, the evidence is sufficient to infer that smoking affects components of the innate and adaptive immune system. Second, evidence shows that cigarette smoke both activates and suppresses certain facets of the immune system. Of note, not every observed detrimental effect of cigarette smoke on components of the immune system will necessarily impact overall immunity. Immune cells respond in concert with other cell types and effector mechanisms; therefore, the effects on specific immune processes may be compensated by other cellular or molecular effector mechanisms. Despite compensatory mechanisms, cigarette smoke's adverse impact on innate and adaptive immune processes may compromise the ability to elicit appropriate immune inflammatory responses to clear harmful environmental agents and maintain tissue homeostasis.

## Effects of Components of Cigarette Smoke on Immunity

The following discussion presents an overview of the effect of a selected few individual components of cigarette smoke on immune function. There is conclusive evidence that the particulate phase of cigarette smoke directly activates phagocytic lung cells, which accounts for some of the proinflammatory effects of smoke. Moreover, gas-phase toxins and oxidants directly damage lipids, proteins, DNA, and organelles and thereby have a proinflammatory effect. Contrasting with these proinflammatory effects, smoke may also exert immune suppressive and anti-inflammatory properties via oxidants, CO, nicotine, and some aromatic compounds. Cigarette smoke can chemically modify signaling pathways and the extracellular matrix, affecting cell activation, differentiation, and survival. While informative, the findings of studies investigating individual components to the overall effect of cigarette smoke on immunity have to be cautiously interpreted, as the net effect of cigarette smoke on the immune system ultimately reflects the sum of the interactions of all of its components exerted over time. Hence, any biological activity observed in isolation may not reflect the compound's effect within the complex mixture, but mechanistic insights are gained.

### Nicotine

There is compelling evidence that nicotine affects cellular immunity, either directly by interacting with nicotinic cholinoceptors or indirectly via its effects on the nervous system. This topic is covered in Chapter 5, "Nicotine" in the section on "Health Consequences of Nicotine Exposure."

### Acrolein

Acrolein is a highly reactive intermediate formed in the context of smoking by combustion and oxidation of lipids in the cell membrane. Acrolein is known for its ability to form protein adducts, bind to DNA, and induce oxidant-dependent damage to cellular structures and organelles. Lambert and colleagues (2005) found that acrolein and crotonaldehyde are the main constituents of the vapor phase that inhibit IL-2, IFN-γ, and TNF-α production by stimulated peripheral blood lymphocytes. This effect is reduced by *N*-acetylcysteine. In a study by Hristova and colleagues (2012), innate immunity was suppressed, similar to that of the direct effects of smoking, in mice exposed for 4 hours to 5 parts per million of acrolein. This effect was prominent in macrophages where impairment of NF-κB production was associated with depressed activation of c-Jun N-terminal kinase (JNK) and activation of c-Jun. Proteomic analysis revealed that acrolein was able to chemically modify recombinant JNK2 by forming protein adducts at CYS41 and CYS177, which are parts of JNK2 thought to be needed to allow activation of mitogen-activated protein kinase binding and JNK2 phosphorylation. In a similar previous study, Lambert and colleagues (2007) found that acrolein-induced suppression of cytokine release was associated with alkylation of cysteine and arginine residues on the NF-κB binding domain, which, presumptively, then reduced the ability of this transcription factor to regulate positively gene expression. Green (1985) showed that acrolein suppressed phagocytosis and antibacterial defenses by alveolar macrophages against staphylococci both in vitro and in vivo. Mechanistically, acrolein can impair primary recognition of LPS by the TLR4 receptor (Lee et al. 2008). The effects of acrolein on epithelium (e.g., suppression of beta-defensins that protect against infections) can occur at concentrations that do not cause overt oxidative stress (Lee et al. 2007c). In pathogen interaction studies, exposure to acrolein after viral infection in vivo markedly worsened the impairment of antibacterial defense caused by virus (Astry and Jakab 1983). In fractionation studies seeking to identify the factor(s) responsible for smoke-induced suppression of lymphocyte proliferation, acrolein was the most prominent cause (Lambert et al. 2005).

Broadly, acrolein has potent suppressive effects on innate and adaptive immune cells both in vitro and in vivo. The effects are observed at a physiologically relevant concentration.

### Polycyclic Aromatic Hydrocarbons

Cigarette smoke contains several polycyclic aromatic hydrocarbons, notably B[*a*]P, that are known agonists of AHR (Löfroth and Rannug 1988; Meek and Finch 1999; Kitamura and Kasai 2007). AHR is a ligand-gated transcription factor that modulates gene expression and is notable for the very low concentration of ligand needed to exert effects. The receptor is widely expressed and in the immune system is prominent in Th17 and dendritic cells. The importance of AHR activation in cancer induction is strongly supported by studies showing that mice lacking this receptor are protected from B[*a*]P-induced carcinogenesis (Shimizu et al. 2000). An important part of carcinogenesis appears to be the HSP90-dependent induction of cytochrome P-450 isoforms that biotransforms the components of cigarette smoke into DNA adduct-forming carcinogens (Hughes et al. 2008).

Seemingly paradoxical, AHR-deficient mice showed enhanced inflammation in response to exposure to smoke (Thatcher et al. 2007). This appeared to result from premature degradation of REL-like, domain-containing protein, which leads to over-activity of NF-κB, a major inflammatory transcription factor. In a study by Head and Lawrence (2009), AHR stimulation in a model of respiratory viral infection using influenza A, was associated with increased neutrophilic inflammation, while the adaptive CD8+ T cell response was suppressed. The latter effects on adaptive immunity were stronger on primary than on memory responses (Lawrence et al. 2006; Neff-LaFord et al. 2007).

IL-17 is an important effector cytokine in the development of sustained neutrophilic inflammatory pathologies. Smoking exerts an adjuvant-like effect via the AHR and has been shown to promote the induction of IL-17A, CCL2, and macrophage activation that in turn promotes the formation of emphysema in mice (Chen et al. 2011). Activation of AHR is strongly implicated in smoke-induced atherosclerosis, likely reflecting dysregulated inflammation (Wu et al. 2011a).

In summary, AHR ligands contained within cigarette smoke exert both proinflammatory and immune-suppressive effects. Of interest is the link between the AHR and IL-17, an important cytokine in neutrophilic inflammatory conditions.

## Carbon Monoxide

Cigarette smoke contains high concentrations of CO. A molecular machinery exists to respond to CO, considering the role of endogenously generated CO as a signaling mediator (Motterlini and Otterbein 2010). Thus, the effects of CO in smoke can be largely understood as an exaggeration of the normal physiological effects of endogenous CO.

Endogenous CO is formed during the catabolism of heme by HMOX, which exists in two forms: inducible heme oxygenase (decycling) 1 protein (HMOX1) mouse and constitutively expressed HMOX2 (Motterlini and Otterbein 2010). Oxidants strongly induce HMOX1, which is likely to play a protective role against oxidant-induced damage. Transcriptional efficiency of HMOX is regulated, in part, by the (GT)n dinucleotide repeat in the 5′-flanking region of the gene; the greater the number of repeats, the weaker the gene induction. A long dinucleotide repeat sequence has been linked to emphysema susceptibility in smokers (Yamada et al. 2000), lung adenocarcinoma (a type of cancer common among people with COPD), and decline of lung function (Kikuchi et al. 2005; Nakayama et al. 2006). Cell culture and in vivo studies showed that HMOX can protect from oxidative stress (Lee et al. 1996; Otterbein et al. 1999).

Coregulation of oxidative stress is not the only known effect of CO, which also protects cells from apoptosis and exerts weak, but real anti-inflammatory and antiproliferative effects in a range of in vivo and in vitro cell models. CO activates the soluble guanylate cyclase/guanosine monophosphate transduction pathway in many different cell types, including immune effector cells. In macrophages, CO inhibits signaling by TLR2, 4, 5, and 9 (but not TLR3) (Song et al. 2003; Nakahira et al. 2006). Here, the mechanism of action of CO is complex: it acts indirectly by suppressing the trafficking of TLRs into lipid-raft signaling complexes in the cell membrane. Evidence also indicates that CO suppresses allograft rejection (Song et al. 2003) via immune suppression, antiproliferative effects, and protection against apoptosis. These effects occur at the higher concentrations (approximately 500 parts per million) that may be encountered during exposure to smoke. Of note, the effects of soluble CO as a signaling molecule are short-lived. However, CO may exert persistent effects via protein carbonylation.

In summary, CO is abundant in cigarette smoke. Although CO protects cells from apoptosis and exerts mild anti-inflammatory and antiproliferative effects, its importance to cigarette smoke's overall effect on the immune system is not well understood.

## Other Mechanisms

### *Protein Derivatization by Oxidants and Chemically Reactive Intermediates*

Oxidants and chemically highly reactive intermediate moieties that are present in cigarette smoke frequently react with proteins (and other critical macromolecules), changing their function through derivatization and formation of consequent structures (such as polymers). Protein modification may also underlay the continuous oxidative stress that is caused by chronic exposure to smoke. Glutathione is one of the main intracellular defenses against oxidation. Under normal conditions, glutathione is reversibly oxidized and can be converted back to itself. Evidence suggests that cigarette smoke may effectively deplete glutathione by forming irreversible glutathione-aldehydes (van der Toorn et al. 2007).

In the context of smoking, *S*-glutathionylation (covalent binding of glutathione to protein thiols, which can be reversed enzymatically by glutaredoxins) and *S*-nitrosylation (modification of protein thiols by nitric oxide, which occurs in a process that can be reversed by the enzyme alcohol dehydrogenase) are common events (Kuipers et al. 2011). However, one of the most important processes of this type is carbonylation, which can be irreversible. Carbonylation is a chemical process where CO is introduced into the chemical structure of target molecules. Kuipers and colleagues (2011) extensively studied the nature of post-translational modifications caused by smoking and found that *S*-glutathionylation and *S*-nitrosylation were both decreased by smoking over a 4-week period, whereas carbonylation increased due to increased oxidative stress. This observation is consistent with the widespread occurrence of carbonylation in the lungs and also in peripheral tissues of smokers (Rahman et al. 2002; Barreiro et al. 2005). Describing the functional consequences of carbonylation for immunity, Bozinovski and colleagues (2011) associated in vitro cigarette smoke-extract mediated carbonylation—not *S*-glutathionylation and *S*-nitrosylation—with decreased TNF-α expression and phagocytosis by mouse alveolar macrophages. Carbonylation can also trigger autoantibody production as it alters the physical structure of proteins and generates neo-antigens, which is one probable link between smoking and autoimmunity (Kirkham et al. 2011). In addition to altering protein structure, carbonylation targets proteins for proteolytic destruction and may lead to pathogenic protein aggregation (Nystrom 2005).

In summary, chemically reactive moieties present in cigarette smoke carbonylate proteins and other macromolecules in smokers and experimental models. Although carbonylation caused by cigarette smoke is associated with

altered macrophage function, further studies are required to understand the biological significance of this effect and determine the specific molecular targets of carbonylation. Chemical modification of the host's proteins can generate neo-antigens, leading to the production of autoantibodies against these chemically modified molecules.

#### *Autophagy and the Unfolded Protein Responses*

Consequences of oxidative damage to protein structure include autophagy and unfolded protein responses (UPRs). Autophagy is a catabolic process during which cellular components are degraded via the lysosome (Ryter et al. 2012). Increased autophagy has been documented electromicrographically in people with COPD and by inference from the expression or activation of autophagy-associated proteins (LC3B, autophagy-related 4 [ATG4], ATG5/12, ATG7) (Chen et al. 2008). Mechanistically, autophagy has been related to smoke-induced decreases in histone deacetylase activity that in turn increase binding of early growth response-1 and E2F factors to the autophagy gene *LC3B* promoter, thus increasing *LC3B* expression. Of note, Monick and colleagues (2010) observed autophagy defects in alveolar macrophages that were isolated from smokers. These defects were associated with impaired protein aggregate clearance, dysfunctional mitochondria, and defective delivery of bacteria to lysosomes, linking autophagy to compromised bacterial host defense.

UPR is normally a homeostatic process that controls stress in the endoplasmic reticulum in response to accumulation of misfolded or unfolded proteins (Hetz 2012). UPR orchestrates the recovery of endoplasmic reticulum function, as failure to adapt to endoplasmic reticulum stress results in apoptosis. Normally the cell responds by slowing protein synthesis and increasing production of molecular chaperones needed for correct protein folding. UPR is prominently induced in the lungs of chronic cigarette smokers, as reflected by upregulation at the protein level of the UPR chaperones, GRP78, calreticulin, and calnexin (Kelsen et al. 2008). While there is evidence that acrolein, a component of cigarette smoke, induces endoplasmic reticulum stress and causes airspace enlargement (Kitaguchi et al. 2012), it is unclear whether UPR is linked to the formation of emphysema. Furthermore, despite accumulating evidence that immune responses can be adversely affected by abnormalities in the UPR (Todd et al. 2008), no formal experimental link has been established between UPR and impaired immunity caused by smoking.

In summary, autophagy and UPR are intrinsic responses to oxidative damage to proteins. Evidence suggests that cigarette smoking is associated with defective autophagy in smokers. These defects compromise bactericidal activity of alveolar macrophages and clearance of modified proteins. Despite evidence that UPR is activated in smokers, whether these processes contribute to impaired immunity is not understood.

## Evidence Synthesis

A wealth of information is available to assess the impact of the individual components of cigarette smoke on immune function. Nicotine exerts both immune stimulatory and suppressive effects directly through receptors expressed on immune cells and indirectly via the nervous system. Acrolein has powerful immune-suppressive effects on innate and adaptive immune cells. Other components, such as AHR ligands, exert both proinflammatory and immune-suppressive effects, but CO has weak but significant anti-inflammatory and antiproliferation effects. Oxidants and chemically reactive intermediates can modify proteins and macromolecules, compromising their function and generating neo-antigens that may drive autoimmune processes.

## Conclusion

1. The evidence is sufficient to infer that components of cigarette smoke impact components of the immune system. Some of these effects are immune activating and others are immune-suppressive.

2. While research on components of smoke is informative, it is difficult to project how an individual component's impact on the immune system relates to its effect within cigarette smoke as a whole. Furthermore, effects observed in isolation may be mitigated by or magnified in the context of exposure to the full mixture of cigarette smoke. Hence, observations made using individual components have to be interpreted cautiously.

## Immunologically Mediated Diseases Associated With Smoking

Exposure to cigarette smoke is a determinant of the incidence, prevalence, and severity of a large number of diseases, whose diathesis is predicated on immunologic dysregulation (Sopori 2002; Stampfli and Anderson 2009). These diseases include diverse viral and bacterial infections, especially but not exclusively of the lungs (invasive pneumococcal disease, pneumonia, influenza, tuberculosis [TB]); periodontal disease; bacterial meningitis; postsurgical infection; rheumatic disorders, especially

rheumatoid arthritis and SLE; Crohn's disease; and cancers (USDHHS 2004, 2010).

Observational evidence shows that smoking may also reduce the incidence of several diseases known to be immunologically mediated, including ulcerative colitis, sarcoidosis, farmer's lung, pigeon breeder's disease, and Sjögren's syndrome (Sopori 2002). Although this duality may seem paradoxical, it is consistent with the complex nature of smoking as both an immunologic stimulant and suppressant. Similarly, the constituents of cigarette smoke can concurrently stimulate and suppress different components of complex immune effector networks.

## Smoking, Immunity, and COPD

COPD is an umbrella term, describing a group of overlapping pathologies that lead to airflow limitation that is largely irreversible (Rabe et al. 2007) (see Chapter 7, "Respiratory Diseases"). The main pathological components of COPD are emphysema (the loss of gas-exchanging lung parenchyma), bronchiolitis (inflammation and fibrosis of small airways), and bronchitis accompanied by airway mucus hypersecretion. The causative role of smoking in the development of COPD is well-established (USDHHS 2004, 2010).

According to widely accepted research, chronic inflammation contributes to airflow limitation seen in COPD (Hogg 2004; Rabe et al. 2007), causing structural changes and narrowing of the small airways. McDonough and colleagues (2011) reported that narrowing and disappearance of small conducting airways precedes the onset of emphysematous destruction in COPD.

This discussion considers only the intersection of smoking, immunity, and COPD and does not consider the general pathobiology of COPD, a topic covered extensively in the 2010 Surgeon General's report (USDHHS 2010). Answers to several broad questions are of interest to the field: how do immune cells contribute to the pathogenesis of COPD; why is immunity persistently weakened and compromised after COPD becomes established; how does this altered immunity contribute to recurrent chest infections that provoke exacerbations; and what is the link between COPD and lung cancer?

## Immune Mechanisms of Cigarette Smoke-Induced Inflammation

Extensive analysis of lungs affected by COPD has revealed that effector cells of both the innate and the adaptive immune system are present in increased numbers in the lungs and show signs of recent activation. Macrophages, neutrophils, and T and B lymphocytes are all increased in various parts of the COPD-affected lung (Finkelstein et al. 1995; Di Stefano et al. 1998, 2004; Saetta et al. 1999; Hogg et al. 2004; Tate et al. 2009; Laws et al. 2010; Singh et al. 2010), and several mediators released by these inflammatory cells likely play a critical role in airflow obstruction by inducing mucus hypersecretion, bronchial constriction, and alveolar destruction. Surface profiling of the lymphocyte population revealed strong enrichment for CD4+ T cells and especially C8+ T cells in smokers and people with COPD (Tsoumakidou et al. 2004).

Although evidence indicates that both adaptive and innate immune components contribute to cigarette smoke-induced inflammation, animal studies using mice carrying the severe combined immunodeficiency mutation, which lack functional T and B cells, have revealed that the presence of an adaptive immune system is not required for smoke-induced inflammation and the formation of emphysema (D'hulst et al. 2005a,b). Studies using *Rag1*-deficient mice that lack functional T and B cells confirmed that innate immune processes are sufficient to elicit cigarette smoke-induced inflammation (Botelho et al. 2010). There is clear evidence that macrophage-derived proteases, such as MMP-12, a potent elastin-degrading enzyme also known as macrophage metalloelastase, and neutrophil-derived proteases, such as neutrophil elastase, contribute to emphysematous lung destruction in mice (Hautamaki et al. 1997; Shapiro et al. 2003).

Findings from other studies seemingly contrast with these findings. In a study by Maeno and colleagues (2007), CD8+ T cell-deficient mice showed a blunted inflammatory response and did not develop airspace enlargement in response to long-term exposure to cigarette smoke. Further confirming an important role for adaptive immune cells, Motz and colleagues (2010) showed that transfer of CD3+ T cells, which were isolated from the lungs of cigarette smoke-exposed mice, to T cell-deficient recipients (*Rag2*-/-) induced substantial pulmonary changes, including monocyte/macrophage and neutrophil accumulation, activation of proteases, and airspace enlargement. While these studies provide evidence that the adaptive immune system can induce disease, further research is required to determine the specificities of T cells activated by cigarette smoke, as this will provide needed information about the processes that drive adaptive immunity.

Taken together, these findings indicate that smoke-induced stimulation of innate and adaptive immunity can cause lung disease. In most affected people, both innate and adaptive immune processes likely contributed to disease, because these systems are highly entwined physiologically. Histological examination revealed that emphysematous changes correlate with macrophage and lymphocyte numbers, especially the number of CD8+ T cells (Majo et al. 2001). Mechanistically, CD8+ T cells can activate macrophages to secreted macrophage matrix MMP-12 (Grumelli et al. 2004).

Mechanisms by which cigarette smoke activates innate and adaptive immunity are less well-understood. Doz and colleagues (2008) demonstrated a critical role of TLR4/MyD88 and IL-1R1/MyD88 signaling in cigarette smoke-induced neutrophilia. While cigarette smoke contains biologically relevant levels of LPS (Hasday et al. 1999), Doz and colleagues (2008) suggested that HSP70, an endogenous TLR4 ligand, may drive smoke-induced neutrophilia. Maes and colleagues (2008) discussed whether the TLR4-dependency was reflective of the short-term exposure protocol utilized in the study by Doz and colleagues (2008).

The IL-1R1-dependency of cigarette smoke-induced inflammation has been consistently observed in several studies (Botelho et al. 2011; Pauwels et al. 2011). More specifically, Churg and colleagues (2009) demonstrated that processes associated with IL-1R1 signaling pathways contributed to the formation of emphysema; IL-1R1-deficient mice had approximately 60% reduced airspace enlargement following prolonged cigarette smoke exposure. Of note, inflammatory processes elicited by cigarette smoke required crosstalk between IL-1α+ hematopoietic and IL-1R1+ nonhematopoietic cells (Botelho et al. 2011). IL-18, another member of the IL-1 family, was also shown to contribute to cigarette smoke-induced inflammation and airspace enlargement (Kang et al. 2007). Expression of IL-1β- and IL-18-induced pulmonary inflammation and emphysema, of which the pathologies of both are associated with COPD (Lappalainen et al. 2005; Kang et al. 2007). While there is convincing evidence that members of the IL-1 family contribute to cigarette smoke-induced inflammation, it is currently not known whether components of cigarette smoke directly activate IL-1 and IL-18 expression or whether DAMPs, secondary to cigarette smoke-induced tissue damage, induce IL-1 and IL-18 expression. The latter is supported by observations from Chen and colleagues (2007a) showing that dying cells elicit inflammation through IL-1 pathways. Evidence suggests that extracellular adenosine triphosphate, a known DAMP, contributes to cigarette smoke-induced inflammation through purinergic receptor signaling in an IL-1-dependent manner (Eltom et al. 2011; Lucattelli et al. 2011; Cicko et al. 2010).

There is conclusive evidence that cigarette smoke activates innate and adaptive immune processes that contribute to the pathogenesis of COPD in susceptible people. While cellular and molecular mechanisms of the pathogenic inflammation associated with COPD are being uncovered in murine models, further research is required to delineate how cigarette smoke activates innate immune processes and target antigens of the adaptive immune response. The latter is of particular interest, because it will provide insight as to whether T and B cells that accumulate in the lungs of smokers are responding to environmental agents, such as viruses and bacteria or potentially attack host tissue.

### Smoking and Respiratory Infections

Cigarette smoking is strongly associated with an increased prevalence and severity of diverse infections (Nuorti et al. 2000; Arcavi and Benowitz 2004). This is especially striking for infections of the respiratory tract where increased risks of pneumonia, invasive pneumococcal disease, influenza, and TB have been identified epidemiologically. Moreover, viral and bacterial infections are a major cause of acute exacerbation of COPD, which punctuates the natural course of this disease (Sethi and Murphy 2001; Wedzicha 2004; Sethi 2005; Donaldson and Wedzicha 2006; Papi et al. 2006; Rabe et al. 2007). Taken together, these studies show that smoking is associated with an increased incidence of microbial infection of the respiratory system, providing evidence that cigarette smoke may compromise respiratory host defense.

### Smoking and Viral Infections

During epidemic influenza A, smoking significantly increased the incidence and severity of influenza in healthy young adults (MacKenzie et al. 1976; Kark et al. 1982) and suppressed vaccine responses (MacKenzie et al. 1976). Exposure to secondhand smoke as a young child was a risk factor for respiratory syncytial virus (RSV) bronchiolitis (Gurkan et al. 2000). Maternal postnatal smoking is an important risk factor for more severe bronchiolitis after RSV infection (Bradley et al. 2005).

Cigarette smoke impacts several key antiviral host defense mechanisms that likely contribute to increased risk of respiratory viral infection. For example, cigarette smoke extract suppressed in vitro antiviral immunity via oxidant-dependent processes at least in part due to hypoactivation of RIG1, an intracellular innate immune sensor that responds to virus (Wu et al. 2011b). Furthermore, cigarette smoke compromised the induction of an antiviral state by suppressing the immediate early phase and the inductive phase of the type I IFN response (Bauer et al. 2008a; Eddelston et al. 2011). Moreover, smoking suppressed T cell responses to influenza (Feng et al. 2011), although more studies are required because this effect was not consistently observed among studies (Robbins et al. 2006). Smoking also directly suppresses the activity of NK cells, weakening antiviral defenses (Mian et al. 2008). Other studies have shown similarly adverse effects of cigarette smoke on responses to viruses by peripheral blood mononuclear cells (Mian et al. 2009) and respiratory epithelial cells (Hudy et al. 2010; Eddleston et al. 2011).

In several animal models of viral infection, smoking adversely affects the normal defensive immune inflammatory response in vivo (Robbins et al. 2006; Gualano et al. 2008; Kang et al. 2008; Botelho et al. 2011). Most studies reported to date have used the influenza virus to examine the consequences of cigarette smoke to antiviral host defense. With the development of a transgenic mouse expressing human *ICAM-1* (Bartlett et al. 2008), which is the receptor for rhinovirus, studies examining the impact of cigarette smoke exposure on rhinovirus infection would be topical, given the clinical data reported for people with COPD who are also infected with rhinovirus (Mallia et al. 2011). The most noteworthy effect was the enhancement of inflammation (Robbins et al. 2006; Gualano et al. 2008; Kang et al. 2008; Botelho et al. 2011), which is associated with increased mortality (Robbins et al. 2006). Moreover, increased numbers of influenza-specific CD8+ T cells were observed in cigarette smoke-exposed mice (Gualano et al. 2008). The heightened inflammatory response was associated with increased inflammatory mediator expression, which in turn accelerated the formation of emphysema (Kang et al. 2008), providing evidence that altered immune defense to viral agents contributes to the pathogenesis of emphysema. Mechanistically, increased inflammation and remodeling was IL-18Rα-dependent, although another study (Botelho et al. 2011) suggested that IL-1R1-dependent activation of the airway epithelium contributes to the exacerbated inflammatory response elicited by influenza virus in smoke-exposed mice. In a study by Gualano and colleagues (2008), exposure to cigarette smoke was associated with a transient increase in viral burden following influenza infection, suggesting that compromised viral clearance may drive the exacerbated inflammatory response. Contrasting with these observations, studies pursued by other research groups did not show increased viral titers in cigarette smoke-exposed influenza-infected animals (Robbins et al. 2006; Kang et al. 2008; Botelho et al. 2011).

To investigate most effectively the effects of cigarette smoking on lung viral host defense, studies such as those published by Mallia and colleagues (2011) are of critical importance. Using a model of controlled rhinovirus infection among human volunteers, the study demonstrated that infection in people with COPD could induce the symptomatic, physiologic, and inflammatory features that have been previously reported in naturally occurring exacerbations of the disease. Rhinovirus infection was associated with an increased neutrophilic inflammation and deficient production of IFN-β. Although this addresses an important and highly relevant question related to acute exacerbations of COPD, the study did not include a nonsmoking control group. Hence, further studies are required to investigate the direct effects of cigarette smoke on immune and inflammatory processes elicited by experimental viral infections. This is an important consideration, as decreased type I IFN levels are not consistently observed in murine models of exposure to smoke (Robbins et al. 2006; Bauer et al. 2010), despite in vitro findings (Bauer et al. 2008a), and it is possible that decreased type I IFN levels are unique to smokers who develop COPD.

In summary, there is conclusive evidence that smoking is associated with an increased risk of respiratory viral infection. Given the complex and multilayered nature of the immune system, it is not known which of cigarette smoke's multiple adverse effects on host defense pathways affect the overall responses to viral agents. Animal studies consistently show that exposure to cigarette smoke exacerbates inflammatory processes elicited by viral infection. Mechanistic studies suggest that members of the IL-1 family, such as IL-1 and IL-18, contribute to this exacerbated inflammatory response. Further evidence suggests that cigarette smoke compromises key innate antiviral host defense mechanisms. Of particular interest are reports in which human volunteers were infected with clinically relevant viral pathogens under controlled experimental conditions. Such an approach will provide important insights into the effects of cigarette smoke antiviral host defense and its importance to the pathogenesis of smoking-related diseases, such as COPD.

### Smoking and Bacterial Infections

Consistent with the increased risk of bacterial infections, cigarette smoke decreases important innate antibacterial defense proteins (Shibata et al. 2008), impairs the ability of macrophages to phagocytose and kill cellular pathogens (King et al. 1988; Berenson et al. 2006; Hodge et al. 2007, 2008), and compromises mucociliary clearance and the integrity of the epithelium (Boucher et al. 1980; Jones et al. 1980; Burns et al. 1989; Dye and Adler 1994). Where long-term smoking has caused organ disease, those organs, especially the lung, manifest further perturbed immunity. This effect relates strongly to exacerbations caused by chest infection in COPD, which can be provoked by both bacteria and viruses (Sethi and Murphy 2001; Wedzicha 2004; Papi et al. 2006).

Altered macrophage function and altered mucociliary clearance may also contribute to microbial colonization of the lungs of smokers, defined in the past by isolation of positive culture and viewed as a consequence of long-term smoking (Patel et al. 2002; Sethi and Murphy 2008). However, more recent metagenomic data have led to a revision of this concept; it is now understood that the healthy "sterile" lung has a bacterial metagenome

(Charlson et al. 2011). A similar bacterial metagenome was observed in healthy nonsmokers and smokers without COPD. In contrast, changes in the lung microbiome were observed in those with severe COPD (Charlson et al. 2010; Hilty et al. 2010; Erb-Downward et al. 2011; Sze et al. 2012). Changes in the microbiome may be confined to a specific area, as significant differences in bacterial communities were observed in people with advanced COPD between different sampling sites (Erb-Downward et al. 2011). Interestingly, metagenomic analysis revealed that smoking has a significant and independent effect on the microbiota of patients with active Crohn's disease (Benjamin et al. 2012), suggesting that the effect of cigarette smoke on the microbiota is observed at sites distant to the lungs.

Studies in animal models have demonstrated that exposure to cigarette smoke exacerbated inflammatory responses elicited by several different bacterial agents, including NTHi, *Pseudomonas aeruginosa (P. aeruginosa)* and *Streptococcus pneumoniae* (*S. pneumoniae*) (Drannik et al. 2004; Gaschler et al. 2009; Phipps et al. 2010; Harvey et al. 2011). In all studies, the cellular composition of the bacteria-exacerbated inflammatory response was neutrophilic in nature. Several of these in vivo models found increased bacterial burden, following bacterial challenge, in cigarette smoke-exposed mice compared with controlled mice (Drannik et al. 2004; Phipps et al. 2010; Harvey et al. 2011), providing evidence that compromised bacterial clearance drives these inflammatory processes. Contrasting with these observations, Gaschler and colleagues (2010) reported that the excessive inflammation observed in cigarette smoke-exposed, NTHi-infected mice was associated with a decreased bacterial burden. Mechanistically, this decrease was linked to increased titres of NTHi-specific IgA antibodies in the bronchoalveolar lavage fluid of cigarette smoke-exposed mice. NTHi-specific antibodies observed in cigarette smoke-exposed mice were likely natural antibodies against conserved bacterial targets that have been shown to protect against nasal colonization with genetically diverse NHTi strains in mice (Zola et al. 2009). Of interest, cigarette smoke-exposed mice expressed a skewed inflammatory mediator profile following NTHi challenge (Gaschler et al. 2009). This altered inflammatory mediator expression was also observed in alveolar macrophages cultured ex vivo, implying a crucial role of alveolar macrophages in mediating this skewed phenotype. Despite the different findings regarding bacterial clearance, increased cellular inflammation was consistently observed in animal models. These data suggest that cigarette smoke skews host defenses against bacteria, leading to exaggerated and possibly damaging inflammatory responses to bacteria.

There is good evidence that viral infections divert local immunity and render the host susceptible to subsequent bacterial infection. Mechanisms proposed through which viral infections predispose to bacterial superinfection include disruption of the respiratory epithelium (Avadhanula et al. 2006), impairment of ciliary function (Jakab and Green 1972; Park et al. 1993), and reduced innate antibacterial function (Jakab and Green 1976; Navarini et al. 2006; Didierlaurent et al. 2008; Shahangian 2009). While viral and bacterial co-infections are a significant cause of COPD exacerbations and are associated with greater lung function impairment and longer hospitalizations (Papi et al. 2006), the interplay between cigarette smoke, virus, and bacteria is an understudied area.

Worldwide, smoking is a leading risk factor associated with acquisition, active disease, and mortality from TB (also see "Tobacco and TB" in Chapter 7, "Respiratory Diseases") (Gajalakshmi et al. 2003; Bates et al. 2007; Slama et al. 2007). Protective immunity to *Mycobacterium tuberculosis (M. tuberculosis),* the causative agent of TB, is dependent on the coordinated innate and adaptive immune response and relies on the generation of a robust type 1 immunity (Ernst 2012). Of note, the consumption of tobacco products has markedly increased in the developing world, where TB is most prevalent. The convergence of these two epidemics makes understanding how exposure to cigarette smoke impacts TB immunity a critical health challenge. Two studies (Feng et al. 2011; Shang et al. 2011) investigated the impact of cigarette smoke on the development of type 1 immunity in the context of *M. tuberculosis* or mycobacterial infection in experimental models. These studies showed a link between exposure to cigarette smoke and impaired type 1 immunity in the lung. The experimental protocol in both studies assessed the impact of prior (discontinued) exposure to cigarette smoke on anti-TB immunity only. To date, no study has evaluated the effect of continuous exposure to cigarette smoke on host defense against pulmonary mycobacterial infection, leaving a critical knowledge gap.

In conclusion, there is clear evidence that compromised bacterial host defense is associated with an increased risk of infection by a range of different bacterial agents, including *S. pneumoniae,* NTHi, *Moraxella catarrhalis,* and *P. aeruginosa,* pathogens commonly associated with COPD exacerbation, as well as *M. tuberculosis.* A range of different immune defects contributes to the increased risk of bacterial infection, including defects in the respiratory epithelium, alveolar macrophage function, and adaptive immunity. The latter is of particular relevance, because it likely contributes to an increased risk of TB in smokers.

## Smoking and Asthma

Asthma is an inflammatory disease of the airways. Conventionally, asthma is viewed as an immunologic disease, in which overactive T cell immunity, specifically Th2 immunity, leads to bronchial inflammation (Robinson et al. 1992; Coyle et al. 1995). This inflammation intersects with genetic predisposition for altered airway function, manifesting in the episodic airflow limitation that is characteristic of the condition. As for other chronic inflammatory lung diseases, patients are prone to recurrent exacerbations triggered by chest infections, which in the case of asthma are almost always caused by a virus, often rhinovirus (Busse et al. 2010). The unifying hypothesis that asthma is a disorder of Th2 immunity has been questioned in recent years, as it does not agree well with clinical observations (Anderson 2008; Holgate and Davies 2009). Asthma manifests in grades of increasing severity. Very severe and refractory asthma, which is by nature resistant to conventional anti-inflammatory therapy, may represent expression of markedly different immune effector pathways, as classical eosinophilic inflammation is less prominent. Neutrophil-rich inflammation is more prominent in severe asthma (or the group of conditions that constitute). The observation of neutrophilic inflammation in severe asthma has been interpreted as evidence of Th17 activity and also as evidence that the inflammation is triggered by innate immunity PRR effector mechanisms (Alcorn et al. 2010).

Epidemiologic studies indicate that exposure to smoke, both in utero and perinatally, increases the risk for asthma (Bouzigon et al. 2008). Noakes and colleagues (2003) associated exposure to smoke with significantly higher neonatal Th2-type responses and early onset asthma. Well-powered population association studies have demonstrated a link between risk for asthma and an asthma susceptibility locus on chromosome 17q21 (Bouzigon et al. 2008), but specific genes contributing to the increased risk and mechanisms of action are not known at present.

Asthmatic smokers are largely understudied, as smoking is often an exclusion criterion for asthma studies and, physiologically, asthmatics who smoke manifest considerable fixed airflow limitation, a disease phenotype that overlaps with COPD. Smoking unequivocally worsens asthma of all grades, accelerates the decline in lung function, and impairs the therapeutic response to corticosteroids (Kerstjens et al. 1993; Chalmers et al. 2002; Chaudhuri et al. 2003). These adverse consequences occur even though smoking suppresses sputum eosinophilia in asthmatic smokers compared with asthmatic nonsmokers (Chalmers et al. 2001). Results of most animal models of experimental asthma mirror this finding (Melgert et al. 2004; Robbins et al. 2005; Thatcher et al. 2008; Trimble et al. 2008), although contrasting findings have been presented (Moerloose et al. 2005). Mechanisms that suppress eosinophilia are currently not well understood. Seemingly contrasting with these findings, exposure to cigarette smoke enhances sensitization to allergens and can bypass or override the normal tolerogenic response to inhaled antigen in mice (Rumold et al. 2001; Moerloose et al. 2006; Trimble et al. 2008). Experimental evidence suggests that this response is mediated, at least in part, through GM-CSF (Trimble et al. 2008). Similar processes likely contribute to the increased risk of asthma observed in young children that are exposed to cigarette smoke (Ehrlich et al. 1996; Jaakkola and Jaakkola 2002). Taken together, this is a further example of the dual nature of smoking as an immune stimulus and as a suppressor, as discussed previously.

Important parallels exist between severe asthma and the impact of cigarette smoke on the immune system. In people with COPD and in smokers without overt lung disease, asthma is associated with functional defects in macrophages (Huynh et al. 2005; Fitzpatrick et al. 2008; Naessens et al. 2012), diminishing their ability to clear and kill pathogens and to remove cellular debris. As discussed previously, compromised clearance of apoptotic cells may contribute to secondary inflammation, as intracellular DAMPs that would otherwise have been contained spill into tissue and promote secondary inflammation. Moreover, innate antiviral responses can be impaired in asthmatics (Wark et al. 2005; Contoli et al. 2006; Edwards et al. 2012). Hence, the adverse effects of cigarette smoke on antimicrobial host defenses may further weaken already compromised host defenses in people with asthma. For this reason, asthma may be more difficult to control in asthmatic smokers than in asthmatic nonsmokers (see Chapter 7).

In summary, the impact of cigarette smoke on the immune system affects multiple facets of the asthma diathesis. Cigarette smoke as an immune stimulator likely facilitates allergic sensitization early in childhood, and deficient antimicrobial host defense contributes to the increased risk of viral and bacterial infection and renders asthma more difficult to control.

## Cigarette Smoke and Autoimmunity

Since the concept was first proposed by Agustí and colleagues (2003), a body of evidence has accumulated to suggest that smoking can lead to autoimmunity at least in the context of severe COPD. Autoimmunity arises when classical tolerance to self-antigens is lost or critically weakened, and T and/or B cell-mediated immune responses attack host tissues (Wing and Sakaguchi 2010).

COPD does not show striking *HLA* restriction, which is often seen for such classical T cell autoimmune diseases as multiple sclerosis and rheumatoid arthritis (Martin et al. 1992). Emerging evidence, however, suggests that the classical signs of B cell-directed autoimmunity—such as antibodies against double stranded DNA and antinuclear antigen, which occur in SLE—are observed following exposure to smoke (Bonarius et al. 2011; Nunez et al. 2011).

A measure of evidence also indicates that adaptive autoimmunity against the lung can be triggered by cigarette smoke. TCR oligoclonality was observed in lung CD4+ and CD8+ T cells of smokers and people with severe emphysema, as well as in cigarette smoke-exposed mice (Korn et al. 2005; Sullivan et al. 2005; Motz et al. 2008). Although suggestive that a narrow range of antigenic epitopes drove expansion, the specificity of these T cells was not assessed and may have included self- or pathogen-derived antigens. To date, studies elutriating MHC I- or MHC II-bound peptides from antigen-presenting cells have not been reported in either animal models or in COPD. Such studies are required to determine if the loaded peptides are self-derived, which would be indicative of an autoimmune process.

The ability of lymphocytes to mount an inflammatory attack is counterregulated by regulatory T cells whose activity is diminished by chronic smoking (Barceló et al. 2008). The number of regulatory T cells is higher in smokers with preserved lung function but diminished in people with COPD. Smoking diminishes forkhead box PC (FOXP3), a transcription factor essential to the development of competent regulatory T cells, in human airways and reduces FOXP3 in people with COPD (Isajevs et al. 2009). These data indicate that regulatory mechanisms that control the function of T cells may be restrained in people who develop COPD.

B cell proliferation and formation of germinal center-like lymphoid aggregates, where oligoclonal expansion of B cells occurs, take place in the lungs of people with COPD, as well as in mice exposed to cigarette smoke (Hogg 2004; van der Strate et al. 2006). B cells (and antibody secreting plasma cells) have been implicated in models of smoke-induced lung damage in which a number of autoantibodies against lung matrix (e.g., elastin) have been observed (Lee et al. 2007a). Lee and colleagues (2007a) ascribed the T cell phenotype as Th1, but according to Ouyang and colleagues (2008), T cell-mediated autoimmunity in other organs suggest that Th17 cells, rather than Th1 cells, are orchestrators of destructive inflammation. Kirkham and colleagues (2011) demonstrated that smoking-induced carbonylation of matrix proteins create neo-antigens that then promote the formation of self-antibodies. The presence of pathogenic complement fixing IgG1 antibodies was associated with damage to blood vessel and endothelial cells.

A concept of autoinnate immunity is emerging in which the innate immune system is inappropriately self-stimulated (Anderson 2008). More than 30 years ago, researchers recognized that lung matrix fragments generated by elastolytic enzymes, such as human neutrophil and porcine pancreatic elastases, are chemotactic for monocytes but not for mature alveolar macrophages or neutrophils (Senior et al. 1980; Hunninghake et al. 1981). A more recent study discovered that these elastin fragments directly activate chemokine receptors and contribute to macrophage accumulation and airspace enlargement following the administration of porcine pancreatic elastase in mice (Houghton et al. 2006). Moreover, evidence suggests that collagen-derived fragments exert neutrophil chemotactic properties in rats (Riley et al. 1988). Hence, proteolytic fragments generated by a net protease/antiprotease imbalance may propagate cigarette smoke-induced inflammation. Of note, IL-1R1/signaling pathways have been implicated in these processes (Couillin et al. 2009).

As discussed previously, cigarette smoke diminishes the capacity of alveolar macrophages to clear cells undergoing programmed cell death (Hodge et al. 2007). Aside from safely clearing moribund cells, efferocytosis prevents immune activation secondary to exposure to DAMPs and alarmins. In mice, clearance of apoptotic neutrophils induces a regulatory phenotype in macrophages that may regulate T cell responses (Filardy et al. 2010). In an oxidant-dependent manner, smoking suppresses efferocytosis by alveolar macrophages (Richens et al. 2009). Further evidence suggests that the accumulation of ceramides—a sphingolipid second messenger associated with cell differentiation, proliferation, and apoptosis—in the lung may contribute to inhibition of apoptotic cell clearance by alveolar macrophages (Petrusca et al. 2010). Defects in efferocytosis may also contribute to the development of autoimmunity in susceptible smokers.

In summary, chronic exposure to cigarette smoke is associated with the emergence of autoreactive T and B cells. Mechanisms that contribute to these autoimmune processes remain to be elucidated, but may include cigarette smoke's adjuvant properties, likely through innate immune stimulation and dendritic cell activation, chemical modification of self-proteins to create neo-antigens, defective clearance of apoptotic cells, and compromised regulatory functions of T cells. Although the evidence suggests that cigarette smoke induces autoimmune processes, the importance of these processes in the expression and progression of smoking-related diseases, such as COPD, remains poorly understood.

## Other Diseases

Smoking cigarettes is a risk factor for developing a number of autoimmune diseases, including rheumatoid arthritis (see subsequent section in this chapter), SLE (see subsequent section in this chapter), multiple sclerosis, Graves' hyperthyroidism, and primary biliary cirrhosis, amongst others (Costenbader and Karlson 2006; Klareskog et al. 2007; Jafari and Hintzen 2011).

### *Multiple Sclerosis*

The association of smoking with multiple sclerosis has been addressed in multiple epidemiological studies. Hernán and colleagues (2001) examined smoking as a risk factor for multiple sclerosis in the two nurses' cohorts. Current smoking was significantly associated with the relative incidence rate of multiple sclerosis (RR = 1.6; 95% CI, 1.2–2.1) (Hernán et al. 2001). The RR increased with greater cumulative exposure of smoking, and RR is not elevated in former smokers. Sundström and colleagues (2008) carried out a nested case-control study in Sweden for 109 people with multiple sclerosis and 218 matched controls. Cotinine levels were measured in samples stored at the start of an intervention study. An elevated level of cotinine was associated with the risk for multiple sclerosis, particularly in women (Sundström et al. 2008).

In a review article, Jafari and Hintzen (2011) described the findings of 14 studies on cigarette smoking and the onset of multiple sclerosis, and 3 studies on cigarette smoking and progression of multiple sclerosis. Most of the studies on cigarette smoking and onset showed a positive association, while the evidence on the 3 studies on progression was limited and mixed.

In a study by Hedström and colleagues (2009), risk for multiple sclerosis was higher in people who smoked cigarettes than in those who used Swedish snuff (snus), which points to the possible significance of reactive intermediates formed during combustion. Smoking is also associated with conversion from a relapse, remitting to a more severe and progressive clinical course (Healy et al. 2009) that is associated with larger and more damaged brain lesions (Zivadinov et al. 2009). Evidence on a potential mechanism is limited (Jafari and Hintzen 2011). In model systems, exposure to smoke directly induced microglial inflammation (Ghosh et al. 2009).

### *Smoking and Cystic Fibrosis*

Cystic fibrosis (CF) is a heritable genetic disease caused by genetic mutations that affect the CF transmembrane conductance regulator (CFTR) (Gadsby et al. 2006). CFTR governs airway hydration and influences innate host defenses such that its impairment leads to lung inflammation, lung colonization with pathogens, recurrent chest infection, impaired lung growth in childhood, progressive decline in lung function in adulthood, impairment of pancreatic function, and reduced fertility. Smoking worsens CF and predisposes people with CF to infection (Campbell et al. 1992; Verma et al. 2001). Smoking results in ciliostasis and decreased function of the chloride channel (Campbell et al. 1992; Cohen et al. 2009), as smoking directly impairs the function of CFTR (Cantin et al. 2006). In a study by Rubin (1990), children with CF who were exposed to secondhand cigarette smoke had a markedly higher hospital admission rate for chest infections and a much worse clinical status than their counterparts. In population studies, exposure of children with CF to cigarette smoke was associated with increased use of intravenous antibiotics, suggesting more severe and possibly more frequent chest infections (Gilljam et al. 1990). As with asthma and COPD, the probable mechanism underlying such results is the suppression of antimicrobial host defenses, which is known to be compromised already in people with CF (Zheng et al. 2003). Of interest, the severity of the effect of smoking on CF is further influenced by gene variants in *TNF*-α, a proinflammatory factor, and *GSTM1*, a gene encoding the detoxifying antioxidant glutathione *S*-transferase M1 (Hull and Thomson 1998).

### *Smoking, HIV, and Immunity*

Smoking is not associated with the progression of HIV disease, as measured by CD4+ cell counts and viral load (Galai et al. 1997; Kabali et al. 2011). However, smoking increases the risk of developing oral candidiasis and bacterial pneumonia in people who have HIV (Conley et al. 1996; Sapkota et al. 2010). Of some interest, metagenomic profiling of tobacco has revealed multiple human pathogens, and some of these can survive tobacco burning and be inhaled (Sapkota et al. 2010). Among smokers, HIV infection appears to compound the risk of developing COPD but the role of altered immunity in this association is uncertain (Petrache et al. 2008). Among human papillomavirus ([HPV] 16 and 18)-infected, HIV-positive smokers, the increased risk of cervical cancer likely relates to the increase in the replication of HPV. While compromised immune status due to HIV contributes to persistent HPV infection, higher HPV16 and HPV18 DNA load was associated with current smoking status (Palefsky et al. 1999; Xi et al. 2009), suggesting a direct effect of cigarette smoke. HIV doubles the risk of liver cancer and this risk is synergistically increased by smoking (Chuang et al. 2010), but it is not known if defective immunity is related to this association.

### Smoking, Immunity, and Cancer

Exposure to cigarette smoke, both active and passive, is an established cause of lung cancer (Kuper et al. 2002; USDHHS 2004, 2010; Stewart et al. 2008) (also see "Changes in Cigarettes and the Risk of Lung Cancer Over Time" in Chapter 6). Long at issue is the extent to which the immune system contributes to this increased cancer risk.

Currently, there is evidence that the effects of cigarette smoking on immunity contribute to cancer in two main ways. First, cigarette smoke is a potent inflammatory stimuli and inflammation is a direct cancer risk (Mantovani et al. 2008; Grivennikov et al. 2010). Second, suppression of immunity by cigarette smoke likely compromises tumor immune surveillance (Stampfli and Anderson 2009).

Development of cancer is a multistage process. In the course of exposure to smoke, the epithelium acquires somatic mutations and molecular defects that culminate in oncogenic transformation. It is widely accepted that inflammatory processes play a critical role in this process (Grivennikov et al. 2010). Takahashi and colleagues (2010) demonstrated that inflammation elicited by exposure to cigarette smoke promotes tumor formation in an IκB kinase β (IKK-β) and JNK1-dependent manner. Reactive oxygen species and nitrogen intermediates, which are produced by activated inflammatory cells, may contribute to DNA damage in addition to smoke's direct DNA damaging effects. Of note, oncogenically mutated epithelium is itself markedly pro-inflammatory and less able to defend against pathogens (Anderson and Bozinovski 2003). Strong evidence indicates that as epithelial cells progressively acquire somatic mutations (e.g., in *KRAS*), inflammation and bacterial burden in the lungs increases (Anderson and Bozinovski 2003; Ji et al. 2006). These somatic mutations also increase the capacity of the epithelium to promote inflammation; for example, they concurrently decrease the ability of the epithelium to contain viral infection (Liu et al. 2008b). These observations may provide links between defects in host defense, increased inflammation, and enhanced risk for cancer.

Pioneering work from Chalmer and colleagues (1975) provided direct experimental support for defects in immune surveillance of transplanted cancers, showing that cell-mediated immune responses to transplanted tumors were inhibited in mice that were chronically exposed to cigarette smoke. Smoke exposure significantly increased the number of lung metastases following tumor challenge (Lu et al. 2007). This effect was reversible following smoking cessation and likely the consequence of impaired NK-cell function. Moreover, prenatal exposure to cigarette smoke decreased offspring resistance against transplanted tumor cells in mice (Ng et al. 2006). This phenomenon was related to decreased T cell-mediated cytotoxicity. The study did not observe an effect of prenatal exposure to cigarette smoke on the activity of NK cells.

About one-half of all surgically resectable, Stage 1 cancers of the lung removed with curative intent prove fatal, because even early stage lung cancer can be highly metastatic (Nagrath et al. 2007; Maheswaran et al. 2008). Aside from inducing cancer, inflammatory processes associated with smoking also promote metastasis from tumors, for example, by inducing matrix degrading proteases such as MMP-9 from mast cells, macrophages, and neutrophils (Alberg et al. 2005). The inflamed lung also forms a receptive field to receive metastases, especially from melanoma, breast, colon, and liver cancers.

In summary, inflammation appears to be a critical link between smoking, the immune system, and lung cancer. In experimental models, there is evidence that smoking compromises tumor immune surveillance. Affected processes include defective activity of NK cells and decreased T cell-mediated cytotoxicity.

### Smoking, Immunity, and Maternal Smoking During Pregnancy

Epidemiologic studies have clearly established the links between adverse prenatal conditions and increased risk for diseases, health problems, and psychological outcomes later in life, and this forms the basis of the Developmental Origins of Health and Disease hypothesis (Gluckman et al. 2008). Maternal cigarette smoking during pregnancy remains a relatively common, but nonetheless hazardous, in utero exposure associated with a range of adverse postnatal and long-term adverse effects (Knopik et al. 2012) (see Chapter 9, "Reproductive Outcomes"). The postulated mechanism linking prenatal and early postnatal environmental exposure with adverse health outcomes later in life is epigenetic programming, such as alterations in DNA methylation (Low et al. 2011).

DNA methylation changes are detectable in blood leukocyte DNA from the umbilical cord in offspring of mothers who smoked during pregnancy. In an epigenome-wide analysis, Joubert and colleagues (2012) showed that genes involved in xenobiotic metabolism (e.g., *AHRR* and *CYP1A1*) and haematopoiesis (e.g., *GIF1, HLA-DPB2,* and *RUNX1*) display altered methylation in blood leukocyte DNA from the umbilical cord in response to maternal cigarette smoking. Such effects may be part of a wider epigenetic influence on fetal growth and child development (Knopik et al. 2012; Haworth et al. 2013). It remains to be established whether such epigenetic changes persist until

adulthood. However, the observation that grandmaternal smoking during pregnancy can result in increased risk of immune-mediated disease—such as asthma in grandchildren—independently of maternal smoking during pregnancy (Li et al. 2005), suggests that epigenetic programming of immune response in response to cigarette smoke may be inherited transgenerationally.

Direct effects on immune system function of smoking by the mother during pregnancy have also been observed. Gene expression in leucocytes from the umbilical cord is altered in response to maternal smoking. Genes showing significant modulation include those related to xenobiotic metabolism, oxidative stress, inflammation, immunity, and hematopoiesis. In particular, functional annotation of the affected genes has identified several deregulated pathways that associated with immune diseases, such as asthma, in the offspring of smokers (Votavova et al. 2011).

In an animal study, Basta and colleagues (2000) showed that rats exposed to nicotine during the gestational period exhibit decreased peripheral blood mononuclear cell proliferative responses to lipopolysaccharide or mitogen-induced activation, in both the early postnatal period and adulthood. In another animal study, involving low-dose exposure to cigarette smoke in pregnant mice, Ng and Zelikoff (2008) observed increased circulating white blood cell and lymphocyte numbers for up to 2.5 months after birth but with decreased mitogen-stimulated T cell proliferation.

In humans, several studies on cord blood have shown changes in immunological variables in smoking compared with nonsmoking mothers. Cord blood has been shown to contain significantly lower levels of polymorphonuclear leukocytes (Mercelina-Roumans et al. 1996) and higher levels of Ig (Cederqvist et al. 1984) in response to prenatal smoking. Maternal smoking also influences fetal immune function with increased fetal IgE and IgD production (Magnusson 1986) and accompanying lymphoproliferative and cytokine responses to allergens (Devereux et al. 2002; Noakes et al. 2003). In one such study, maternal smoking was associated with lower serum concentrations of IL-4 and IFN-γ in cord blood and a higher risk of wheeze at 6 years of age (Macaubas et al. 2003). Infants born to smoking mothers also showed significant attenuation of innate Toll-like-receptor responses compared with infants of nonsmokers, with implications for the well-recognized increased risk of respiratory infections and asthma in offspring of smoking mothers (Noakes et al. 2006).

## Evidence Synthesis

Collectively, the large body of available evidence reinforces the underappreciated role of cigarette smoke's adverse effects on the immune system in contributing to the causation of disease in smokers. Broadly, cigarette smoke exerts both proinflammatory and immune suppressive effects, which collectively contribute to an increased risk for diseases associated with immune diathesis.

## Conclusions

1. The evidence is sufficient to infer that cigarette smoking compromises the immune system and that altered immunity is associated with increased risk for pulmonary infections.

2. The evidence is sufficient to infer that cigarette smoke compromises immune homeostasis and that altered immunity is associated with an increased risk for several disorders with an underlying immune diathesis.

## Implications

The preceding discussion stresses the complex nature of smoking as both a stimulant and suppressive agent for the functioning of the immune system and outlines the disease processes, cellular effectors, and molecular mechanisms underlying these effects. A greater understanding of the multipartite nature of the effects of smoking on immunity will lead to a better understanding of the ways in which smoking causes disease. Nonetheless, smoking has documented adverse effects on the immune system that may contribute to the general morbidity experienced by smokers.

# Rheumatoid Arthritis and Systemic Lupus Erythematosus

The causes of autoimmune diseases, such as rheumatoid arthritis (RA) and SLE, remain elusive despite considerable research on risk factors and mechanisms. Although there are clearly genetic factors predisposing to these diseases, environmental factors also play a key role in their development (Klareskog et al. 2011; Salliot 2011; Sestak 2011). To date, there is a considerable body of literature on the effect of smoking on RA and a smaller number of studies exploring a role for smoking in SLE. These findings are supported on a mechanistic basis by the findings of studies on smoking and the immune system (see the "Immune Function and Autoimmune Diseases" section in this chapter). This topic, smoking and autoimmune diseases, has not been reviewed previously in the reports of the Surgeon General.

## Description of the Literature Review

An initial search of English publications in PubMed was performed using the key words smoking OR tobacco AND rheumatoid arthritis and then, separately, using the key words smoking OR tobacco AND systemic lupus erythematosus. Similar searches were conducted using the Ovid and Google Scholar Databases and the lists obtained from each search mechanism were compared for duplicate titles. Titles and abstracts were then reviewed for studies that addressed the association between smoking and the development, management, or severity of these diseases. All studies addressing this topic, including review articles and meta-analyses as well as small studies were assessed. In the evidence tables, only studies with more than 50 participants and those presenting original data were included. The literature search extended from 1962 through December 2012.

## Rheumatoid Arthritis

RA is a chronic inflammatory disease of uncertain etiology. Deforming arthritis is the hallmark of RA, but its systemic nature is manifested by the involvement of many other organs including skin, eyes, lungs, blood vessels, and bone marrow. The estimated annual incidence of RA is approximately 40 per 100,000 persons with a prevalence of 1% (Alamanos et al. 2006). RA is more common in women and about 70% of patients are seropositive, as defined by the presence of rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP) (De Rycke 2004). RA is currently treated with a group of immunomodulatory drugs, such as corticosteroids, methotrexate, leflunomide, and inhibitors of TNF-α.

### Biologic Basis

The effect of smoking as a risk factor for RA is mainly observed in RF-positive people with RA and anti-citrulline antibody (Klareskog et al. 2007). RF is a type of antibody directed against the receptor binding Fc region of IgG. As such, RF causes the formation of immune aggregates that are highly proinflammatory. Citrullination (also called deimination) refers to the amino acid arginine that is converted into the amino acid citrulline. Citrullination can alter the tertiary structure of proteins and may give rise to autoantigens that provoke the formation of anti-citrullinated protein antibodies or anti-cyclic citrullinated protein antibodies. In RA, these autoantibodies are frequently made against filaggrin and may cross-react with keratin and perinuclear factor. The direct effect of smoking on immune effector pathways is suggested by the strong association with the major histocompatibility *HLA-DRB1* allele and antibodies directed against citrullinated peptide.

### Evidence Review

There is considerable evidence that smoking is one of several risk factors for the development of RA (Table 10.14*S*). This association was first identified in a study of RA among users of oral contraceptives (Vessey et al. 1987), and has now been replicated in multiple subsequent studies.

Indeed, cigarette smoking has been cited as the most conclusively established environmental risk factor for seropositive RA (Costenbader and Karlson 2006). The risk attributable to smoking among patients of European ancestry has been estimated as approaching one of six (Criswell et al. 2002) and even one of four affected people (Costenbader et al. 2006). Compared with never smokers, smoking is associated with a 1.4–4-fold increased risk of developing RA. Although there is some heterogeneity among the results of these studies, there is consistent evidence that smoking is a stronger risk factor for RA in men than in women. Some studies show that smoking is associated with a younger age at disease onset, and while both intensity and duration of cigarette exposure are associated with increased risk, duration of smoking may have

a larger effect (Costenbader and Karlson 2006). Although a small number of studies directly address risks from secondhand smoke, there is little evidence to suggest that this exposure is a risk factor for development of RA (Soderlin et al. 2013).

Sugiyama and colleagues (2010) confirmed several of these observations in a meta-analysis exploring the effect of smoking on RA. The authors pooled data from 18 studies to examine the effect of cigarette smoking on RF and anti-CCP positive disease, as well as to assess dose-response relationships of cumulative smoking with RA. The summary overall risk for developing RA was 1.4 (95% CI, 1.25–1.58) for ever smokers, 1.35 (95% CI, 1.17–1.55) for current smokers, and 1.25 (95% CI, 1.10–1.40) for past smokers in comparison with never smokers. Although 94% of the patients included in this analysis were women, the strongest risk appeared to be for men, in whom the summary overall risk for current smokers was 1.89 (95% CI, 1.56–2.34), and for RF-positive RA, in whom the overall risk was 3.91 (95% CI, 2.78–5.50). A dose-response relationship was present in women with an overall risk of 1.75 (95% CI, 1.42–2.02) for women with more than a 20-pack year exposure. There were not enough data points to assess the risk of smoking on anti-CCP positivity, but newer clinical studies support this association (Klareskog et al. 2006; Karlson et al. 2010; Kallberg et al. 2011).

There is a growing literature investigating the interaction between genotypes and environmental exposures in RA. Recent work confirms previous studies (Karlson et al. 2010; Mikuls et al. 2010) demonstrating a synergistic effect of smoking with the *HLA-DRB1 shared epitope-containing allele* in RA (Too et al. 2012). A strong association also exists supporting a synergistic effect of smoking and PTPN22, a regulatory component of T cell signaling (Costenbader et al. 2008). The association with anti-CCP positivity and smoking in some ethnic groups with this genetic predisposition is particularly notable (Pedersen et al. 2006; Klareskog et al. 2011; Salliot et al. 2011). Cigarette smoking has also been postulated to increase RA severity, but this association remains controversial. There is some support for an association of smoking with increased radiographic scores, incident rheumatoid pulmonary disease, and decreased overall physical function scores (Table 10.15*S*). For example, Manfredsdottir and colleagues (2006) demonstrated increased disease activity, as assessed by physical exam and history during 2 years of observation in smokers compared to nonsmokers, but smoking was not associated with radiographic progression of disease. Weak evidence suggests that smoking may be a risk factor for formation of rheumatoid nodules (Nyhall-Wahlin et al. 2006). Similarly, several studies showed an effect of smoking on the risk of developing extra-articular manifestations of RA (Kim et al. 2008c; Moura et al. 2012), particularly lung disease. Finckh and colleagues (2007) showed a protective effect of heavy cigarette smoking on RA progression. Differences in patient characteristics and the recent recommendations for early aggressive treatment of RA complicate interpretation of these findings.

In contrast, there is strong evidence that smoking reduces the effectiveness of some therapies for RA (Table 10.16*S*). The response to the TNF-α inhibitory drugs, which are being increasingly used, has been most extensively studied, as drug trials included large numbers of well-characterized patients. Canhão and colleagues (2012) demonstrated that smoking was a strong predictor of a poor response (as measured by European League Against Rheumatism scores) in patients beginning their first TNF-α inhibitor. Other studies show that smoking is associated with reduced likelihood of a good response to TNF-α therapy, with response rates for former smokers falling in between those for never smokers and current smokers (Hyrich et al. 2008; Mattey et al. 2009; Abhishek et al. 2010; Soderlin et al. 2012). Westhoff and colleagues (2008) used changes in medication regimens as a surrogate for poor therapeutic response, and showed that regimen changes occurred more commonly in smokers with RA than in nonsmokers with RA. Medication changes may also occur because of side effects, and one small study of leflunomide lung toxicity demonstrated increased risk of developing lung toxicity in smokers on leflunomide (Inokuma et al. 2008). There is no association of smoking with methotrexate-induced lung toxicity (Beyeler et al. 1996; Cottin et al. 1996).

## Evidence Synthesis

The available evidence supports a causal association of smoking with risk for seropositive RA. There is consistency of the findings over multiple studies involving different populations and large numbers of patients. A clear dose-response with extent of smoking is observed in the majority of studies, and the decline of risk with cessation of smoking also supports causality. There is little evidence to suggest that behaviors associated with smoking, such as alcohol and coffee intake, lower body weight, or poor physical conditioning, contribute to RA; so the association with smoking is not likely to be from confounding. The finding that patients with certain genetic backgrounds are particularly sensitive to the effects of cigarette smoke implies that particular mechanisms could underlie a causal association. Considered with the increasing evidence for a clear biological basis for alterations in the immune system, a causal association between RA and smoking is biologically plausible as well.

Evidence on smoking as a cause of increased disease severity in RA remains conflicting, and is inadequate to infer such a relationship. The studies investigating this association are heterogeneous in their design; some involved only a small numbers of patients; and there is no uniform definition of disease severity. There is sufficient evidence from large and well-designed studies to support the hypothesis that smoking is causally associated with a poor response to TNF-α inhibitors in RA patients. Dose-response relationships were found in many studies and a reduction of risk with smoking cessation further corroborates the significance of this association.

### Conclusions

1. The evidence is sufficient to infer a causal relationship between cigarette smoking and rheumatoid arthritis.

2. The evidence is sufficient to infer that cigarette smoking reduces the effectiveness of the tumor necrosis factor-alpha (TNF-α) inhibitors.

### Implications

Current evidence supports a causal association of smoking with RA and reduced effectiveness of the TNF-α inhibitors. Although overall attributable risk may depend on genetic factors, smoking may be one of the few known modifiable risk factors for the development of RA.

## Systemic Lupus Erythematosus

SLE is an autoimmune disorder that typically affects the skin and joints, but in its most virulent form, SLE may cause severe damage of essential organs including the kidneys and the nervous system. SLE is more common in women than men and more often affects African American and Asian women. This population also tends to have more severe disease. The pathogenesis of SLE is extremely complex and remains elusive. Although deficiencies of complement component genes are associated with a higher incidence of SLE and suggest a strong genetic etiology, concordance rates for SLE in monozygotic twins are only between 25–60% (Sestak et al. 2011). The interplay between environment and genes is considered an important determinant of disease development (Tsokos 2011). A search for additional environmental factors influencing SLE development implicated smoking as a possible trigger.

### Biologic Basis

Smoking is especially associated with the formation of dsDNA antinuclear autoantibodies (Freemer et al. 2006), which are known to induce many of the manifestations of SLE. The dual nature of smoking as an immune-suppressant and immune-activating agent was observed when SLE-prone MLR-*lpr*/*lpr* mice were exposed to cigarette smoke (Rubin et al. 2005). Antinuclear antibodies were suppressed in active smoke-exposed mice. Following smoking cessation, the suppression initially persisted but eventually greater levels of autoantibodies were observed. The study did not assess mechanisms or consequences of altered antibody levels.

### Evidence Summary

Table 10.17*S* summarizes the results of studies, which included 50 or more patients and examined the association between cigarette smoking and the risk of SLE. Eight case-control studies demonstrated a positive association of current smoking with the diagnosis of SLE, while four studies showed no clear evidence of an association. Two of the studies appear to report on many of the same patients (Kiyohara et al. 2012a,b). The second of these studies also evaluated the *CYP1A1* genotype in smokers and is the first study to identify this genotype as having more than an additive effect with cigarette smoking for the development of SLE. An earlier study from the same research group reported an increased risk in a population of Japanese smokers with SLE in one city, but no increased risk in patients from another city in Japan (Washio et al. 2006). Of the two cohort studies, one found a weak association between SLE and smoking (Formica et al. 2003), while the second (Sanchez-Guerrero et al. 1996) showed no association with current or former smoking. In the studies that assessed dose-response with tobacco exposure, a relationship was found in only a single study (Hardy et al. 1998).

A meta-analysis of cigarette smoking and the risk of SLE reported in 2004, included seven case-control studies and two cohort studies (Costenbader et al. 2004). The authors reported an odds ratio of 1.5 (95% CI, 1.09–2.08) for current smokers, as compared to never smokers, for the development of SLE. A sensitivity analysis was performed excluding the study by Ghaussy and colleagues (2001) in which the effect size was much higher than the other studies. With this exclusion, the summary odds ratio was 1.31 (95% CI, 1.01–1.70). The Ghaussy and colleagues study was performed in a predominantly Hispanic population in the Southwest, and thus, may not be representative of the general population with SLE. Three of

the other positive studies included in Table 10.17*S* were carried out in Japan.

Table 10.18*S* summarizes the studies evaluating the impact of smoking on disease severity in people with SLE. It also includes several studies which explore this issue in individuals with only cutaneous lupus erythematosus. Most of the reports focus on cutaneous disease in persons with lupus, among whom smoking is clearly associated with more severe disease that is more difficult to control. The report by Ghaussy and colleagues (2003) on 111 cases demonstrates higher disease activity scores (as measured by the popular Systemic Lupus Erythematosus Disease Activity Index [SLEDAI]) in current smokers as compared to former or never smokers. In contrast, Rahman and colleagues (1998) reported no effect of smoking on SLEDAI scores in a group of 36 persons. Smoking is associated with a higher risk of thrombosis and earlier development of end-stage renal disease in patients with lupus nephritis. The finding of a significantly higher risk of autoantibodies to double-stranded DNA in current smokers suggests that alteration of self-antigens by smoking and immune activation may lead to worsening disease in current smokers. A large study of 1,346 well-characterized SLE patients in Canada reported that current smoking was associated with active SLE rash with an OR of 1.63 (95% CI, 1.07–2.48). Ever smoking was also a risk factor for cutaneous involvement, and increased risk for discoid rash (OR = 2.36; 95% CI, 1.69–3.29) and photosensitivity (OR = 1.47; 95% CI, 1.11–1.95) (Bourré-Tessier et al. 2013).

Table 10.19*S* summarizes the findings on the effect of smoking on the efficacy of treatments for SLE. In 1998, Rahman and colleagues (1998) first described the adverse effect of smoking in patients with cutaneous lupus either alone, or in the setting of SLE, on hydroxychloroquine efficacy. The study included 17 smokers and compared their responses to therapy with those of 19 nonsmokers. Nine of the nonsmokers had complete resolution of their rash within 6 months of treatment with hydroxychloroquine, while only 3 of the smokers had complete resolution. Table 10.19*S* includes two studies, which evaluated treatment in 50 or more patients. One study showed 90% of nonsmokers responded to therapy as compared to only 40% of smokers (Jewell and McCauliffe 2000). The second study evaluated the effect of smoking and *CYP* genotype on response to therapy and found that neither had a significant influence on response (Wahie et al. 2011). A report of 36 persons with cutaneous lupus supports the negative effect of smoking (Kreuter et al. 2009). The authors also reported that cessation of smoking during the observation period improved response to treatment.

## Evidence Synthesis

The current mixed evidence is inadequate to support a causal association between SLE and cigarette exposure. Seven studies found an association, while four studies did not. Reflecting the relative rarity of SLE, many of the studies are small and underpowered. Genetic propensities to SLE remain poorly defined, but the observation of an interaction in risk between smoking and ethnic ancestry, particularly in persons of Hispanic and Japanese descent, suggests a biologic basis for this association. Across heterogeneous populations of SLE patients, however, the effect of smoking may be diluted by the presence of many genotypes. Dose-response relationships were not found in several studies, but sample size and power are limitations of some studies. Similarly, there is inadequate evidence to support a role for smoking as leading to greater severity of SLE. The study populations are small and heterogeneous. More importantly, variations in the definition of disease severity prevent a definitive conclusion. The best evidence supports smoking as a risk factor for cutaneous disease, and there is sparse evidence of an association with earlier renal failure and thrombosis. Similarly, studies showing higher levels of anti-dsDNA antibodies in SLE patients, who currently smoke, as compared to never and former smokers, warrant confirmation.

Finally, there is inadequate evidence supporting an effect of smoking on the response to therapy in SLE.

## Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between cigarette smoking and systemic lupus erythematosus (SLE), the severity of SLE, or the response to therapy for SLE.

## Implications

There is intriguing evidence for an association of smoking with SLE. As few modifiable risk factors for SLE have been identified, further research on smoking and risk for SLE is warranted. Because this life-threatening disease lacks effective specific therapies and is associated with premature cardiovascular disease, continued education of SLE patients on the importance of smoking cessation is recommended.

# Inflammatory Bowel Disease

The predominant forms of inflammatory bowel disease (IBD) are Crohn's disease and ulcerative colitis. Crohn's disease is characterized by transmural inflammation occurring anywhere in the luminal gastrointestinal tract predominately affecting the ileum of the small intestine and the large intestine. In contrast, inflammation associated with ulcerative colitis is generally limited to the mucosal surface of the large intestine, although backwash ileitis can occur with active disease in the cecum.

The reported incidence of IBD is greater in North America and Northern Europe than in other regions of the world where incidence has been evaluated. The incidence of Crohn's disease in North America ranges between 4–16 cases per 100,000 compared with 4–10 in Northern Europe, 1–5 in Southern Europe, and 0–4 in Africa, Asia, and Latin America.

The incidence of ulcerative colitis per 100,000 ranges between 2–16 cases in North America, 3–20 in Northern Europe, 2–11 in Southern Europe, and 1–9 in Africa, Asia, and Latin America (Molodecky et al. 2012). Using the prevalence estimates for North America and a U.S. population of 300 million, the current prevalence of IBD in the United States is estimated at 1.6–1.7 million persons (Molodecky et al. 2012).

Although the incidence of IBD increased during the last century (Binder 2004), the causes of the increase are unknown. Over 160 genetic risk factors have been associated with Crohn's disease and ulcerative colitis (Jostins et al. 2012), but genes alone cannot explain the rapid increase in incidence. While increased diagnostic sensitivity may contribute to the increase, environmental factors, including cigarette smoking, may play a role.

Risk factors for IBD may include cigarette smoking, appendectomy, diet, infections and antibiotics to treat them, and socioeconomic factors (Ng et al. 2013). The environmental factors may interact with genetic risk factors in the development and response of the immune system. Environmental factors may also alter the intestinal microbiome, which also affects IBD (Erickson et al. 2012).

A personal history of cigarette smoking is the best described risk factor for IBD in adults. The first reports of a discordant relationship between active smoking and Crohn's disease and ulcerative colitis were published in the late 1970s and early 1980s (Samuelsson 1976; Mayberry et al. 1978; Harries et al. 1982; Jick and Walker 1983; Logan et al. 1984; Somerville et al. 1984) showing that ulcerative colitis patients were less likely to smoke on or after diagnosis, compared with controls, and more likely to be former smokers than controls. Crohn's disease patients were more likely to smoke on or after diagnosis than controls. A recent meta-analysis reported a protective association of smoking with ulcerative colitis (OR = 0.58) and an adverse association with Crohn's disease (OR = 1.75) (Mahid et al. 2006). A meta-analysis of prenatal and childhood exposure to secondhand cigarette smoke found no association with Crohn's disease or with ulcerative colitis (Jones et al. 2008). Persons with Crohn's disease, who continue to smoke, exhibit a greater need for use of immunosuppressant therapy, have higher rates of surgical resection, and greater frequency of postoperative recurrence after surgery and requirement for repeat resection (Birrenbach and Bocker 2004; Cosnes 2008). An intervention study demonstrated that Crohn's disease patients who stop smoking have a reduction in their need for immunosuppressants or surgery within the first year following cessation of cigarette smoking, when compared with those who continued to smoke. In contrast, cessation of cigarette smoking is sometimes associated with worsening disease activity in ulcerative colitis (Beaugerie et al. 2001; Cosnes 2004, 2008).

## Conclusions of Previous Surgeon General's Reports

The relationship between smoking and IBD has not been assessed in previous Surgeon General's reports.

## Biologic Basis

Many of the Crohn's disease and ulcerative colitis genes are associated with regions encoding immunologic cell functioning including bacterial recognition, signaling, and autophagy. For example, *NOD2* (also known as *CARD15*) genetic polymorphism located on the *IBD1* locus of chromosome 16 is associated with an increased risk of Crohn's disease, but not ulcerative colitis (Hugot et al. 1996, 2001; Ogura et al. 2001). In studies done in epithelial cell lines, cigarette smoke extract affected NOD2 expression and function (Aldhous et al. 2011).

Smoking has widespread effects on immune function. Smoking has a demonstrated role in promoting proinflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8, and GM-CSF, decreasing the anti-inflammatory cytokine IL-10 and activating macrophage and dendritic cell pathways (Arnson et al. 2010), all of which could play a role

in promoting an inflammatory process. Patients with IBD have been demonstrated to have a dysbiosis of the gut microbiome, characterized by a reduced bacterial diversity and a reduction in certain phylogenetic groups (Morgan et al. 2012). Studies have suggested that smoking may alter the composition of intestinal microbiome (Benjamin et al. 2012), and, through it, the risk of Crohn's disease and ulcerative colitis. Smoking may increase colonic mucin production, which may be deficient in ulcerative colitis, but there is no other strong supporting evidence for a mechanism by which smoking plays a protective role (Gibson and Muir 2005).

Despite both diseases sharing the vast majority of the genetic risk loci, the reason for the divergent effect of cigarette smoking on Crohn's disease and ulcerative colitis is unclear. In a study by Bergeron and colleagues (2012), mononuclear cells from Crohn's disease patients had an impaired response against anti-inflammatory and oxidative stress protection, partly through reduced synthesis of heat-shock protein 70. In contrast, similar cells from ulcerative colitis patients and controls did not demonstrate this impaired functioning. Similarly, the differences in the gut microbial consumption in smokers may favor the development of Crohn's disease (Benjamin et al. 2012).

## Epidemiologic Evidence

Studies for the current review were compiled by searching the MEDLINE database accessed through PubMed using the search phrase (smok* or tobacco) and (crohn or "ulcerative colitis" or "inflammatory bowel disease"). The search was performed on January 25, 2013, with no restriction on the date of publication, and 1,102 articles were identified. References cited in relevant reviews and meta-analyses (Cope et al. 1986; Calkins 1989; Thomas et al. 1998; Rubin and Hanauer 2000; Birrenbach and Bocker 2004; Wolf et al. 2004; Mahid et al. 2006; Jones et al. 2008; Bastida and Beltran 2011; Hovde and Moum 2012), and the studies that met the inclusion criteria were checked to identify articles not captured by the search.

Eight studies were excluded because the controls had irritable bowel syndrome or other gastrointestinal conditions (Burns 1986; Cope et al. 1986; Silverstein et al. 1989; Martins et al. 1996; Reif et al. 2000; de Saussure et al. 2007; Mahid et al. 2007; Lopez-Serrano et al. 2010). One study was excluded because the article could not be translated into English (Bures and Fixa 1985). When several articles reported on the same group of cases, the most recent article with the largest sample size and most rigorous control for confounding was included in the analysis (45 duplicates excluded).

Meta-analyses were performed using a random effects model accounting for the type of IBD, study design, and smoking definition. Smoking was classified as current at diagnosis of IBD (and corresponding age or date in controls); current at recruitment for prospective studies or when the questionnaire was administered after IBD diagnosis (or date of questionnaire administered to controls); and ever smoker at diagnosis, the time of the questionnaire, or unspecified smoking definition. Never smoker or not current smoking was used as the comparison. Former smoking was classified at the same time points as current smoking. Information on dose-response is described, but no meta-analyses were performed on dose-response relationships.

Seventy-two studies, which were reported in 75 articles, met the inclusion criteria (Table 10.20*S*). The case-control studies included hospital-based controls (often patients in orthopedic clinics or with fractures admitted through the emergency department), case-nominated controls, or controls that lived near the cases based on hospital or government records. Five prospective cohorts and 1 nested case-control study examined the incidence of Crohn's disease and ulcerative colitis by smoking status (Vessey et al. 1986; Logan and Kay 1989; Tragnone et al. 1993; Carlens et al. 2010; Higuchi et al. 2012; Chan et al. 2013). An additional case-control study enrolled only incident cases (Corrao et al. 1998). Three case series compared smoking among cases with nationally representative estimates (Srivasta et al. 1993; Tuvlin et al. 2007; van der Heide et al. 2011). The majority of studies were conducted in Europe and North America. Some studies included only women because the cases were originally collected to examine the relationship between oral contraceptives or hormone replacement therapy and disease (Vessey et al. 1986; Lashner et al. 1989, 1990; Logan and Kay 1989; Sandler et al. 1992; Katschinski et al. 1993; Boyko et al. 1994; Higuchi et al. 2012).

### Current Smoking

Examining the 53 studies that reported on Crohn's disease, cases were more likely than controls to be current or ever smokers (RR = 1.6; 95% CI, 1.5–1.8). When studies that defined smoking as current at the time of recruitment into a prospective cohort or at the time of diagnosis or symptom onset in case-control studies were combined, the relationship between smoking and Crohn's disease was even greater (RR = 1.8; 95% CI, 1.6–2.2; N studies = 24; Figure 10.7); and the effect estimate did not differ meaningfully by study design. With restriction to studies assessing smoking on or before diagnosis and that adjusted for

**Figure 10.7 Relationship between smoking on or before the time of diagnosis and risk of Crohn's disease**

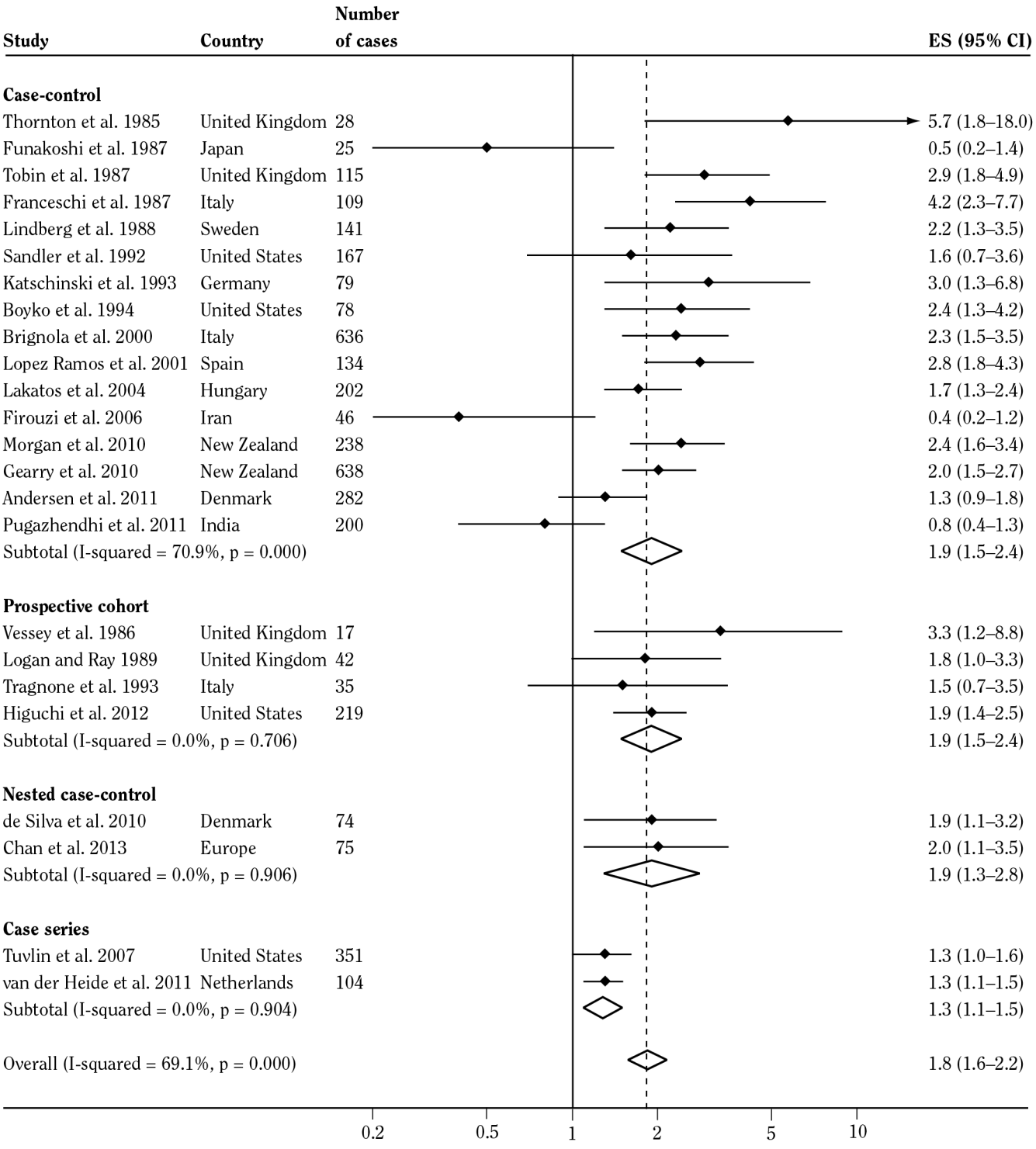


**Figure 10.7 Continued**

| Study | Adjustments |
|---|---|
| **Case-control** | |
| Funakoshi et al. 1987 | Age |
| Tobin et al. 1987 | Age; Gender; Location, region, or center |
| Franceschi et al. 1987 | Age; Gender; Education or social class; Former smoking; Body mass index; Other |
| Lindberg et al. 1988 | Age; Gender; Location, region, or center |
| Sandler et al. 1992 | Oral contraceptives or hormone replacement therapy |
| Katschinski et al. 1993 | Age; Oral contraceptives or hormone replacement therapy |
| Lopez Ramos et al. 2001 | Age; Gender; Education or social class; Tonsillectomy or appendectomy; Oral contraceptives or hormone replacement therapy |
| Firouzi et al. 2006 | Age; Gender; Tonsillectomy or appendectomy; Non-steroidal anti-inflammatory drugs; Oral contraceptives or hormone replacement therapy |
| Gearry et al. 2010 | Age; Gender; Race or ethnicity; Education or social class; Family history of inflammatory bowel disease |
| **Prospective cohort** | |
| Higuchi et al. 2012 | Age; Gender; Body mass index; Oral contraceptives or hormone replacement therapy |
| **Nested case-control** | |
| Chan et al. 2013 | Age; Gender; Location, region, or center |

*Note:* Weights are from random effects analysis. **CI** = confidence interval; **ES** = effect size.

at least one factor in a multivariable model, the association increased (RR = 2.0; 95% CI, 1.6–2.6; N studies = 11). The 2006 meta-analysis by Mahid and colleagues reported an effect estimate of 1.8 (95% CI, 1.4–2.2; N studies = 9) for current smoking combining all studies identified without restriction by timing of current smoking or confounding control.

Sixty-one studies reported on the relationship between current or ever smoking and ulcerative colitis. Ulcerative colitis cases were less likely to smoke than controls (RR = 0.54; 95% CI, 0.48–0.61). Restricting to the 28 studies that reported smoking on or before diagnosis, there was no meaningful change in the point estimate, although the CI was wider (RR = 0.56; 95% CI, 0.45–0.70) (Figure 10.8). With restriction to studies assessing smoking on or before diagnosis and adjusting for at least one factor, there was no meaningful difference compared with the unadjusted studies (RR = 0.49; 95% CI, 0.35–0.66; N studies = 16). The 2006 meta-analysis by Mahid and colleagues reported an effect estimate of 0.58 (95% CI, 0.45–0.75; N studies = 13) for current smoking among all studies identified without restriction to timing of current smoking or confounding control.

When the U.S. studies were compared separately (Jick and Walker 1983; Boyko et al. 1987, 1994; Lashner et al. 1989, 1990; Sandler et al. 1992; Silverstein et al. 1994; Minocha and Raczkowski 1997; Tuvlin et al. 2007; Higuchi et al. 2012), the Crohn's disease and ulcerative colitis results were consistent with the analyses including all countries.

The descriptive epidemiology of IBD in Asia shows rising rates of ulcerative colitis during recent decades when smoking has also increased. When the studies conducted in Asia were considered separately both Crohn's disease (RR = 0.8; 95% CI, 0.6–1.1; N studies = 8) and ulcerative colitis (RR = 0.4; 95% CI, 0.3–0.6; N studies = 13) cases were less likely to smoke than controls (Stermer et al. 1985; Funakoshi et al. 1987; Higashi et al. 1991; Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan [EGRCIBD-Japan] 1994; Nakamura and Labarthe 1994; Reif et al. 1995, 2000; Fich et al. 1997; Naganuma et al. 2001; Firouzi et al. 2006; Jiang et al. 2007; Pugazhendhi et al. 2011; Habashneh et al. 2012; Kayahan et al. 2012). With restriction to studies assessing smoking on or before diagnosis and adjusting

**Figure 10.8 Relationship between smoking on or before the time of diagnosis and risk of ulcerative colitis**

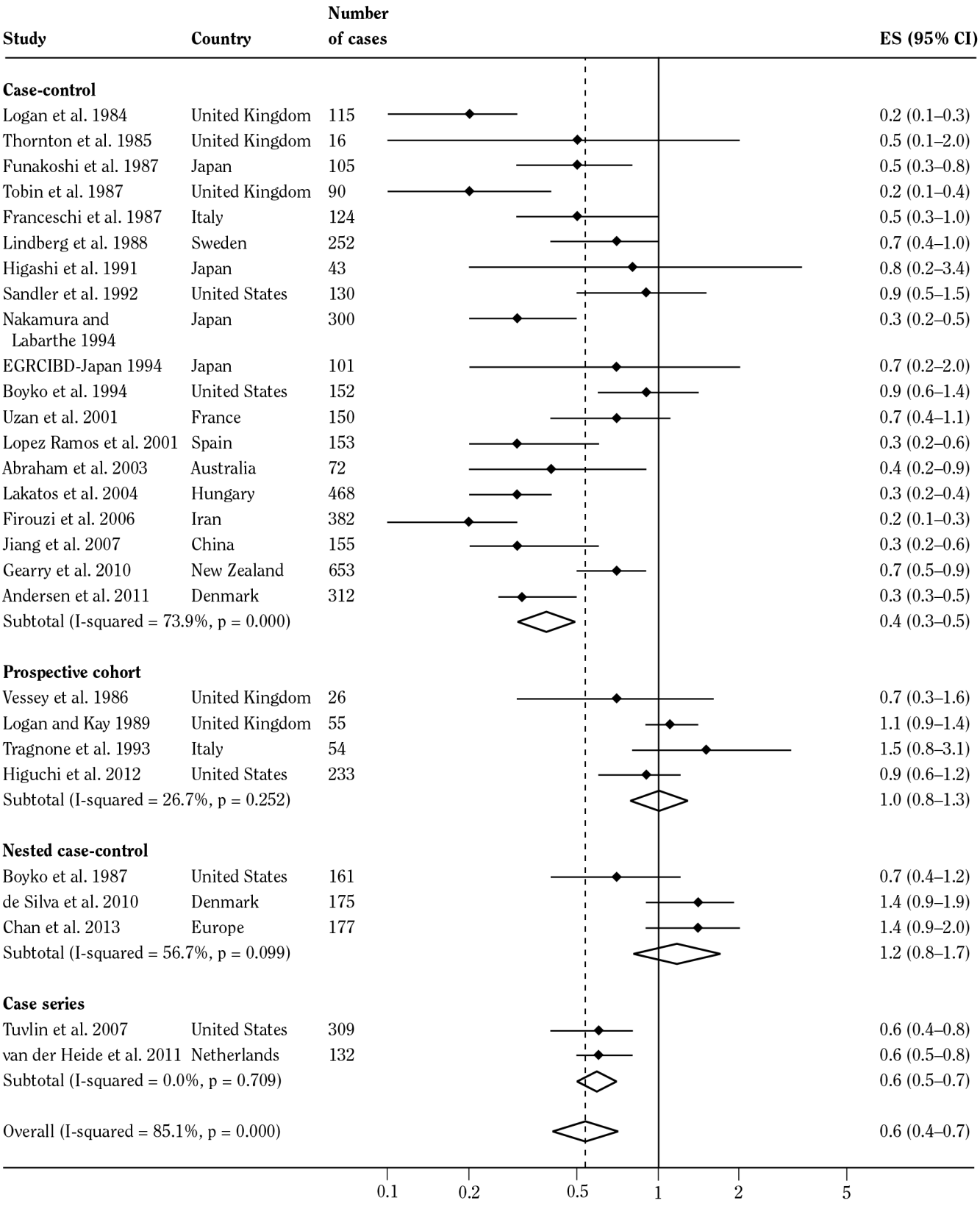


**Figure 10.8 Continued**

| Study | Adjustments |
|---|---|
| **Case-control** | |
| Logan et al. 1984 | Age; Gender; Location, region, or center |
| Funakoshi et al. 1987 | Age |
| Tobin et al. 1987 | Age; Gender; Location, region, or center |
| Franceschi et al. 1987 | Age; Gender; Education or social class; Former smoking; Body mass index; Other |
| Lindberg et al. 1988 | Age; Gender; Location, region, or center |
| Sandler et al. 1992 | Age; Gender; Education or social class |
| Nakamura and Labarthe 1994 | Age; Gender; Alcohol |
| EGRCIBD-Japan 1994 | Age; Gender; Location, region, or center; Alcohol |
| Uzan et al. 2001 | Age; Gender; Location, region, or center; Tonsillectomy or appendectomy |
| Lopez Ramos et al. 2001 | Age; Gender; Education or social class; Tonsillectomy or appendectomy; Oral contraceptives or hormone replacement therapy |
| Firouzi et al. 2006 | Age; Gender; Tonsillectomy or appendectomy; Non-steroidal anti-inflammatory drugs; Oral contraceptives or hormone replacement therapy |
| Jiang et al. 2007 | Age; Gender; Family history of inflammatory bowel disease; Former smoking; Tonsillectomy or appendectomy; Alcohol; Coffee or tea; Diet |
| Gearry et al. 2010 | Age; Gender; Race or ethnicity; Education or social class; Family history of inflammatory bowel disease |
| **Prospective cohort** | |
| Higuchi et al. 2012 | Age; Gender; Body mass index; Oral contraceptives or hormone replacement therapy |
| **Nested case-control** | |
| Boyko et al. 1987 | Age; Gender; Alcohol; Coffee or tea |
| Chan et al. 2013 | Age; Gender; Location, region, or center |

*Note:* Weights are from random effects analysis. **CI** = confidence interval; **EGRCIBD-Japan** = Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan; **ES** = effect size.

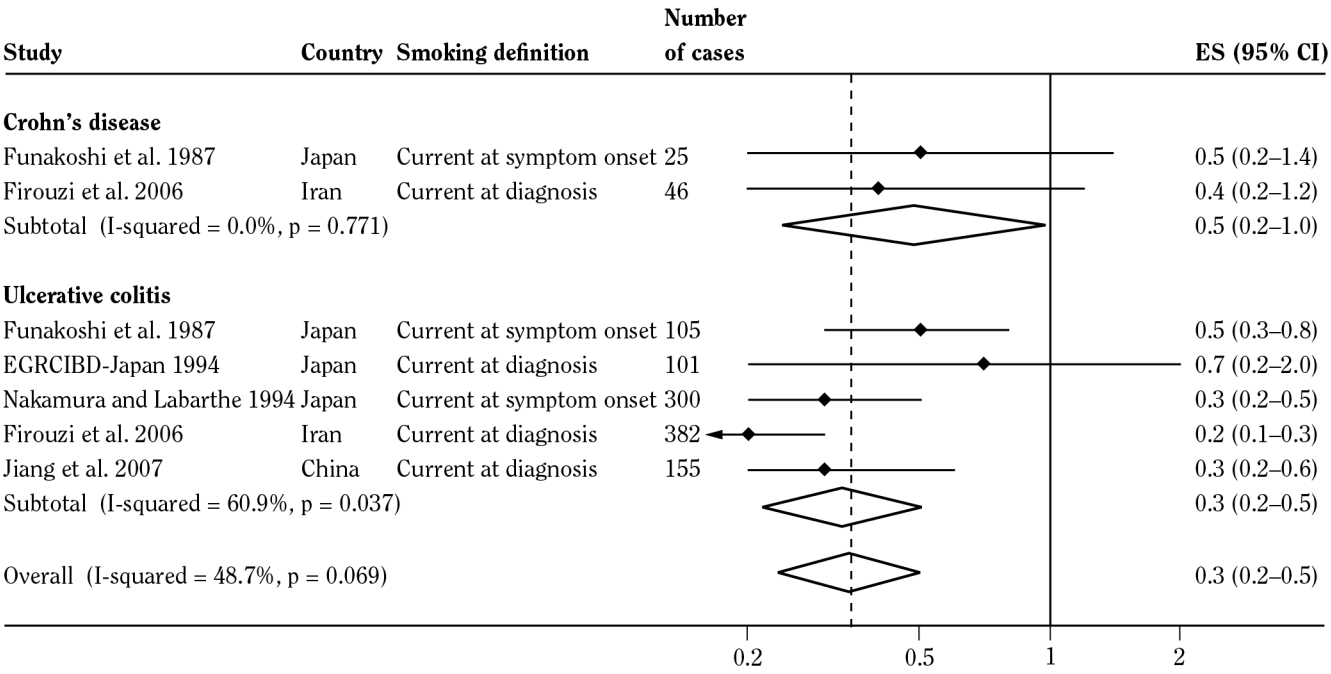
for at least one potential confounding factor, the association with Crohn's disease became statistically significant (RR = 0.5; 95% CI, 0.2–1.0; p = 0.04; N studies = 2) and remained similar to the unadjusted estimate for ulcerative colitis (RR = 0.3; 95% CI, 0.2 – 0.5; N studies = 5) (Figure 10.9).

## Former Smoking

Seventy-one studies reported on the relationship between former smoking and Crohn's disease or ulcerative colitis (Table 10.21*S*). The effect estimates were elevated for both Crohn's disease (RR = 1.3; 95% CI, 1.1–1.5; N studies = 28) and ulcerative colitis (RR = 1.5; 95% CI, 1.3–1.8; N studies = 43). When studies that considered former smoking on or before diagnosis and adjusted for at least one factor were examined, the relationship for Crohn's disease was no longer statistically significant (RR = 1.2; 95% CI, 0.7–1.9; N studies = 6), but the relationship with ulcerative colitis remained statistically significant (RR = 1.7; 95% CI, 1.4–2.1; N studies = 14). The increase in risk of ulcerative colitis in former smokers may persist for as long as 20 years after cessation of smoking (Higuchi et al. 2012). The 2006 meta-analysis by Mahid and colleagues found similar relationships for Crohn's disease (RR = 1.3; 95% CI, 1.0–1.8; N studies = 9) and ulcerative colitis (RR = 1.8; 95% CI, 1.4–2.3; N studies = 13).

When the U.S. and Asian studies were considered separately, the Crohn's disease and ulcerative colitis results were consistent with the analyses including all countries.

**Figure 10.9 Relationship between smoking on or before the time of diagnosis and risk of Crohn's disease or ulcerative colitis among case-control studies conducted in Asia**




| Study | Adjustments |
|---|---|
| **Crohn's disease** | |
| Funakoshi et al. 1987 | Age |
| Firouzi et al. 2006 | Age; Gender; Tonsillectomy or appendectomy; Non-steroidal anti-inflammatory drugs; Oral contraceptives or hormone replacement therapy |
| **Ulcerative colitis** | |
| Funakoshi et al. 1987 | Age |
| EGRCIBD-Japan 1994 | Age; Gender; Location; region or center; Alcohol |
| Nakamura and Labarthe 1994 | Age; Gender; Alcohol |
| Firouzi et al. 2006 | Age; Gender; Tonsillectomy or appendectomy; Non-steroidal anti-inflammatory drugs; Oral contraceptives or hormone replacement therapy |
| Jiang et al. 2007 | Age; Gender; Family history of inflammatory bowel disease; Former smoking; Tonsillectomy or appendectomy; Alcohol; Coffee or tea; Diet |

*Source:* Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan (EGRCIBD).
*Note:* **CI** = confidence interval; **ES** = effect size.

## Dose-Response

Seven studies reported a p-value associated with a test for trend for risk with the number of cigarettes smoked per day or week or pack-years (Jick and Walker 1983; Boyko et al. 1987; Funakoshi et al. 1987; Tobin et al. 1987; Logan and Kay 1989; Nakamura and Labarthe 1994; Higuchi et al. 2012). For Crohn's disease, two studies reported that heavy smokers or current smokers with more pack-years had increased incidence of disease (Logan and Kay 1989; Higuchi et al. 2012). Among former smokers, more pack-years of cumulative smoking was also associated with an increased incidence of Crohn's disease (Higuchi et al. 2012). A dose-response relationship with ulcerative colitis was also rarely reported. Three studies

found that more cigarettes per day or pack-years among current smokers were associated with a decreased risk (Funakoshi et al. 1987; Logan and Kay 1989; Nakamura and Labarthe 1994), but two studies found that heavier current smoking was associated with an increased risk of ulcerative colitis (Jick and Walker 1983; Tobin et al. 1987). Among former smokers, heavier smoking was associated with increased risk of ulcerative colitis in two studies (Boyko et al. 1987; Nakamura and Labarthe 1994). For nine studies, the authors reported no dose-response relationship with the amount of current smoking for Crohn's disease or ulcerative colitis, but did not report a p-value from a test for trend (Boyko et al. 1987; Sorensen et al. 1987; Lindberg et al. 1988; EGRCIBD-Japan 1994; Silverstein et al. 1994; Corrao et al. 1998; Reif et al. 2000; Jiang et al. 2007; Carlens et al. 2010).

## Evidence Synthesis

Smoking could plausibly affect the occurrence of IBD, a group of disorders involving immune mechanisms. However, more specific mechanistic considerations await additional research; and current understanding is insufficient to explain why smoking would increase risk for Crohn's disease and decrease risk for ulcerative colitis.

The observational findings are consistent in showing an increased risk for Crohn's disease with the exception of studies conducted in Asia. Crohn's disease cases were more likely to smoke, or be former smokers, than their comparison groups with the exception of studies conducted in Asia where Crohn's disease cases were less likely to smoke. When studies from all countries were pooled, the findings were consistent across definitions of smoking and in analyses that adjusted for at least one potential confounder. Analyses, in which the timing of smoking was established as antecedent to disease onset, provided the strongest associations, particularly when potential confounding was taken into account. In contrast, ulcerative colitis cases were less likely to be current smokers and more likely to be former smokers at the time of diagnosis, even when at least one potential confounder was accounted for in the analysis.

The associations of smoking with Crohn's disease and ulcerative colitis are moderate in strength (RR = 1.8, and 0.6, respectively), and almost uniformly consistent even when temporality is accounted for. However, the evidence was less supportive for other elements of the guidelines for causal inference. Dose-response relationships were infrequently reported, and the trends of risk were not consistently found to be statistically significant for either Crohn's disease or ulcerative colitis.

A meta-analysis of randomized trials of nicotine replacement therapy did not find that such therapies were effective treatments for ulcerative colitis, although there were issues related to tolerability and adherence in these studies (Nikfar et al. 2010). The negative evidence from trials may also be interpreted as suggesting that nicotine dosing is not the mechanism by which cigarette smoke affects risk of ulcerative colitis.

## Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and Crohn's disease.

2. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and a protective effect for ulcerative colitis.

## Implications

Additional research is needed on the mechanisms by which smoking affects the risk for IBD, particularly the role of gene and smoking interactions given the large number of genetic risk factors. There is no basis for considering smoking as a potential strategy for the prevention of ulcerative colitis, given the uncertainty as to the role of smoking in the pathogenesis of the disease and the increased risk for Crohn's disease associated with smoking. Further review of the impact of smoking on the clinical course of Crohn's disease and ulcerative colitis is warranted.

# Chapter Conclusions

## Eye Disease: Age-Related Macular Degeneration

1. The evidence is sufficient to infer a causal relationship between cigarette smoking and neovascular and atrophic forms of age-related macular degeneration.

2. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of advanced age-related macular degeneration.

## Dental Disease

1. The evidence is suggestive but not sufficient to infer a causal relationship between active cigarette smoking and dental caries.

2. The evidence is suggestive but not sufficient to infer a causal relationship between exposure to tobacco smoke and dental caries in children.

3. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and failure of dental implants.

## Diabetes

1. The evidence is sufficient to infer that cigarette smoking is a cause of diabetes.

2. The risk of developing diabetes is 30–40% higher for active smokers than nonsmokers.

3. There is a positive dose-response relationship between the number of cigarettes smoked and the risk of developing diabetes.

## Immune Function and Autoimmune Disease

1. The evidence is sufficient to infer that components of cigarette smoke impact components of the immune system. Some of these effects are immune activating and others are immune-suppressive.

2. The evidence is sufficient to infer that cigarette smoking compromises the immune system and that altered immunity is associated with increased risk for pulmonary infections.

3. The evidence is sufficient to infer that cigarette smoke compromises immune homeostasis and that altered immunity is associated with an increased risk for several disorders with an underlying immune diathesis.

## Rheumatoid Arthritis

1. The evidence is sufficient to infer a causal relationship between cigarette smoking and rheumatoid arthritis.

2. The evidence is sufficient to infer that cigarette smoking reduces the effectiveness of the tumor necrosis factor-alpha (TNF-$\alpha$) inhibitors.

## Systemic Lupus Erythematosus

1. The evidence is inadequate to infer the presence or absence of a causal relationship between cigarette smoking and systemic lupus erythematosus (SLE), the severity of SLE, or the response to therapy for SLE.

## Inflammatory Bowel Disease

1. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and Crohn's disease.

2. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and a protective effect for ulcerative colitis.

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**Appended Data Table for Figure 10.1**

| Study | Relative risk (95% CI) | Weight (%) |
|---|---|---|
| Keen et al. 1982 | 1.18 (0.44–3.15) | 0.22 |
| Rimm et al. 1995 | 1.96 (1.5–2.56) | 1.78 |
| Kawakami et al. 1997 | 2.51 (1.3–4.84) | 0.46 |
| Njolstad et al. 1998 | 0.82 (0.59–1.13) | 1.42 |
| Sugimori et al. 1998 | 1.42 (1.1–1.83) | 1.88 |
| Uchimoto et al. 1999 | 1.47 (1.13–1.92) | 1.80 |
| Manson et al. 2000 | 1.63 (1.5–1.77) | 3.63 |
| Nakanishi et al. 2000 | 2.90 (1.67–5.03) | 0.63 |
| Strandberg and Salomaa 2000 | 1.62 (1.01–2.59) | 0.81 |
| Hu et al. 2001 | 1.30 (1.15–1.47) | 3.21 |
| Wannamethee et al. 2001 | 1.74 (1.24–2.44) | 1.34 |
| Will et al. 2001 (females) | 1.07 (1.03–1.11) | 3.98 |
| Will et al. 2001 (males) | 1.19 (1.15–1.24) | 3.98 |
| Montgomery and Ekbom 2002 | 2.40 (1.34–4.3) | 0.57 |
| Bonora et al. 2004 | 0.91 (0.52–1.6) | 0.61 |
| Carlsson et al. 2004 | 1.06 (0.87–1.30 | 2.36 |
| Eliasson et al. 2004 | 3.76 (1.52–9.32) | 0.26 |
| Sairenchi et al. 2004 (females) | 1.39 (1.20–1.61) | 2.93 |
| Sairenchi et al. 2004 (males) | 1.27 (1.16–1.39) | 3.59 |
| Foy et al. 2005 | 2.15 (1.20–3.86) | 0.57 |
| Lyssenko et al. 2005 | 1.50 (1.07–2.1) | 1.33 |
| Patja et al. 2005 | 1.41 (1.26–1.57) | 3.35 |
| Tenenbaum et al. 2005 | 1.94 (1.16–3.25) | 0.70 |
| Waki et al. 2005 (females) | 1.42 (0.95–2.12) | 1.05 |
| Waki et al. 2005 (males) | 1.25 (1.07–1.47) | 2.80 |
| Harding et al. 2006 | 1.15 (0.90–1.46) | 1.98 |
| Houston et al. 2006 | 1.65 (1.28–2.13) | 1.88 |
| Meisinger et al. 2006 (females) | 1.38 (1.03–1.84) | 1.62 |
| Meisinger et al. 2006 (males) | 1.69 (1.34–2.13) | 2.07 |
| Burke et al. 2007 | 2.05 (1.23–3.40) | 0.72 |
| Cugati et al. 2007 | 1.57 (1.03–2.40) | 0.96 |
| Dehghan et al. 2007 | 1.16 (0.96–1.40) | 2.48 |
| Holme et al. 2007 | 1.15 (0.93–1.42) | 2.25 |
| Hur et al. 2007 | 1.60 (1.29–1.98) | 2.25 |
| Mozaffarian et al. 2007 | 1.60 (1.34–1.91) | 2.63 |
| Onat et al. 2007 | 0.60 (0.41–0.87) | 1.17 |
| Schulze et al. 2007 | 1.90 (1.47–2.46) | 1.85 |
| Hayashino et al. 2008 | 1.99 (1.30–3.05) | 0.94 |
| Lyssenko et al. 2008 | 1.39 (1.23–1.57) | 3.21 |
| Magliano et al. 2008 | 1.66 (1.11–2.49) | 1.02 |

**Appended Data Table for Figure 10.1 Continued**

| Study | Relative risk (95% CI) | Weight (%) |
|---|---|---|
| Nagaya et al. 2008 | 1.10 (0.96–1.26) | 3.06 |
| Nichols et al. 2008 | 1.37 (1.22–1.54) | 3.28 |
| Park et al. 2008 | 1.73 (1.22–2.46) | 1.25 |
| Chien et al. 2009 | 1.01 (0.83–1.22) | 2.46 |
| Cho et al. 2009 | 2.20 (1.50–3.22) | 1.12 |
| Cullen et al. 2009 | 1.35 (1.20–1.51) | 3.29 |
| Hippisley-Cox et al. 2009 (females) | 1.27 (1.23–1.31) | 4.00 |
| Hippisley-Cox et al. 2009 (males) | 1.25 (1.21–1.29) | 4.02 |
| Mozaffarian et al. 2009 | 1.30 (1.04–1.63) | 2.10 |
| Laaksonen et al. 2010 | 1.78 (1.20–2.65) | 1.06 |
| Yeh et al. 2010 | 1.31 (1.04–1.65) | 2.08 |
| Overall (I-squared = 81.7%, p = 0.000) | 1.37 (1.31–1.44) | 100 |

*Note:* **CI** = confidence interval.

**Appended Data Table for Figure 10.7**

| Study | Design | Country | Number of cases | Effect size (95% CI) | Adjustments |
|---|---|---|---|---|---|
| Thornton 1985 | Case-control | United Kingdom | 28 | 5.7 (1.8–18.0) | — |
| Funakoshi 1987 | Case-control | Japan | 25 | 0.5 (0.2–1.4) | Age |
| Tobin 1987 | Case-control | United Kingdom | 115 | 2.9 (1.8–4.9) | Age; gender; location, region, or center |
| Franceschi 1987 | Case-control | Italy | 109 | 4.2 (2.3–7.7) | Age, gender, education or social class, former smoking, body mass index, other |
| Lindberg 1988 | Case-control | Sweden | 141 | 2.2 (1.3–3.5) | Age; gender; location, region, or center |
| Sandler 1992 | Case-control | United States | 167 | 1.6 (0.7–3.6) | Oral contraceptives or hormone replacement therapy |
| Katschinski 1993 | Case-control | Germany | 79 | 3.0 (1.3–6.8) | Age; oral contraceptives or hormone replacement therapy |
| Boyko 1994 | Case-control | United States | 78 | 2.4 (1.3–4.2) | — |
| Brignola 2000 | Case-control | Italy | 636 | 2.3 (1.5–3.5) | — |
| Lopez Ramos 2001 | Case-control | Spain | 134 | 2.8 (1.8–4.3) | Age; gender; education or social class; tonsillectomy or appendectomy; oral contraceptives or hormone replacement therapy |
| Lakatos 2004 | Case-control | Hungary | 202 | 1.7 (1.3–2.4) | — |
| Firouzi 2006 | Case-control | Iran | 46 | 0.4 (0.2–1.2) | Age; gender; tonsillectomy or appendectomy; non-steroidal anti-inflammatory drugs; oral contraceptives or hormone replacement therapy |
| Morgan 2010 | Case-control | New Zealand | 238 | 2.4 (1.6–3.4) | — |
| Gearry 2010 | Case-control | New Zealand | 638 | 2.0 (1.5–2.7) | Age, gender, race/ethnicity, education or social class, family history of inflammatory bowel disease |
| Andersen 2011 | Case-control | Denmark | 282 | 1.3 (0.9–1.8) | — |
| Pugazhendhi 2011 | Case-control | India | 200 | 0.8 (0.4–1.3) | — |
| Subtotal: Case-control (I-squared = 70.9%; p = 0.000) | | | | 1.9 (1.5–2.4) | |

**Appended Data Table for Figure 10.7 Continued**

| Study | Design | Country | Number of cases | Effect size (95% CI) | Adjustments |
|---|---|---|---|---|---|
| Vessey 1986 | Prospective cohort | United Kingdom | 17 | 3.3 (1.2–8.8) | — |
| Logan 1989 | Prospective cohort | United Kingdom | 42 | 1.8 (1.0–3.3) | — |
| Tragnone 1993 | Prospective cohort | Italy | 35 | 1.5 (0.7–3.5) | — |
| Higuchi 2012 | Prospective cohort | United States | 219 | 1.9 (1.4–2.5) | Age, gender, body mass index, oral contraceptives or hormone replacement therapy |
| Subtotal: Prospective cohort (I-squared = 0.0%; p = 0.706) | | | | 1.9 (1.5–2.4) | |
| de Silva 2010 | Nested case-control | Denmark | 74 | 1.9 (1.1–3.2) | — |
| Chan 2013 | Nested case-control | Europe | 75 | 2.0 (1.1–3.5) | Age; gender; location, region, or center |
| Subtotal: Nested case-cohort (I-squared = 0.0%; p = 0.906) | | | | 1.9 (1.3–2.8) | |
| Tuvlin 2007 | Case series | United States | 351 | 1.3 (1.0–1.6) | — |
| van der Heide 2011 | Case series | Netherlands | 104 | 1.3 (1.1–1.5) | — |
| Subtotal: Case series (I-squared = 0.0%; p = 0.904) | | | | 1.3 (1.1–1.5) | |
| Overall (I-squared = 69.1%; p = 0.000) | | | | 1.8 (1.6–2.2) | |

Note: CI = confidence interval.

**Appended Data Table for Figure 10.8**

| Study | Design | Country | Number of cases | Effect size (95% CI) | Adjustments |
|---|---|---|---|---|---|
| Logan et al. 1984 | Case-control | United Kingdom | 115 | 0.2 (0.1–0.3) | Age; gender; location, region, or center |
| Thornton et al. 1985 | Case-control | United Kingdom | 16 | 0.5 (0.1–2.0) | — |
| Funakoshi et al. 1987 | Case-control | Japan | 105 | 0.5 (0.3–0.8) | Age |
| Tobin et al. 1987 | Case-control | United Kingdom | 90 | 0.2 (0.1–0.4) | Age; gender; location, region, or center |
| Franceschi et al. 1987 | Case-control | Italy | 124 | 0.5 (0.3–1.0) | Age, gender, education or social class, former smoking, body mass index, other |
| Lindberg et al. 1988 | Case-control | Sweden | 252 | 0.7 (0.4–1.0) | Age; gender; location, region, or center |
| Higashi et al. 1991 | Case-control | Japan | 43 | 0.8 (0.2–3.4) | — |
| Sandler et al. 1992 | Case-control | United States | 130 | 0.9 (0.5–1.5) | Age, gender, education or social class |
| Nakamura and Labarthe 1994 | Case-control | Japan | 300 | 0.3 (0.2–0.5) | Age, gender, alcohol |
| EGRCIBD-Japan 1994 | Case-control | Japan | 101 | 0.7 (0.2–2.0) | Age; gender; location, region or center; alcohol |
| Boyko et al. 1994 | Case-control | United States | 152 | 0.9 (0.6–1.4) | — |
| Uzan et al. 2001 | Case-control | France | 150 | 0.7 (0.4–1.1) | Age; gender; location, region or center; tonsillectomy or appendectomy |
| Lopez Ramos et al. 2001 | Case-control | Spain | 153 | 0.3 (0.2–0.6) | Age, gender, education or social class, tonsillectomy or appendectomy, oral contraceptives or hormone replacement therapy |
| Abraham et al. 2003 | Case-control | Australia | 72 | 0.4 (0.2–0.9) | — |
| Lakatos et al. 2004 | Case-control | Hungary | 468 | 0.3 (0.2–0.6) | — |
| Firouzi et al. 2006 | Case-control | Iran | 382 | 0.2 (0.1–0.3) | Age, gender, tonsillectomy or appendectomy, non-steroidal anti-inflammatory drugs, oral contraceptives or hormone replacement therapy |
| Jiang et al. 2007 | Case-control | China | 155 | 0.3 (0.2–0.6) | Age, gender, family history of inflammatory bowel disease, former smoking, tonsillectomy or appendectomy, alcohol, coffee or tea, diet |

**Appended Data Table for Figure 10.8 Continued**

| Study | Design | Country | Number of cases | Effect size (95% CI) | Adjustments |
|---|---|---|---|---|---|
| Gearry et al. 2010 | Case-control | New Zealand | 653 | 0.7 (0.5–0.9) | Age, gender, race/ethnicity, education or social class, family history of inflammatory bowel disease |
| Andersen et al. 2011 | Case-control | Denmark | 312 | 0.3 (0.3–0.5) | — |
| Subtotal: Case-control (I-squared = 73.9%; p = 0.000) | | | | 0.4 (0.3–0.5) | |
| Vessey et al. 1986 | Prospective cohort | United Kingdom | 26 | 0.7 (0.3–1.6) | — |
| Logan and Kay 1989 | Prospective cohort | United Kingdom | 55 | 1.1 (0.9–1.4) | — |
| Tragnone et al. 1993 | Prospective cohort | Italy | 54 | 1.5 (0.8–3.1) | — |
| Higuchi et al. 2012 | Prospective cohort | United States | 233 | 0.9 (0.6–1.2) | Age, gender, body mass index, oral contraceptives or hormone replacement therapy |
| Subtotal: Prospective cohort (I-squared = 26.7%; p = 0.252) | | | | 1.0 (0.8–1.3) | |
| Boyko et al. 1987 | Nested case-control | United States | 161 | 0.7 (0.4–1.2) | Age, gender, alcohol, coffee or tea |
| de Silva et al. 2010 | Nested case-control | Denmark | 175 | 1.4 (0.9–1.9) | — |
| Chan et al. 2013 | Nested case-control | Europe | 177 | 1.4 (0.9–2.0) | Age; gender; location, region, or center |
| Subtotal: Nested case-cohort (I-squared = 56.7%; p = 0.099) | | | | 1.2 (0.8–1.7) | |
| Tuvlin et al. 2007 | Case series | United States | 309 | 0.6 (0.4–0.8) | — |
| van der Heide et al. 2011 | Case series | Netherlands | 132 | 0.6 (0.5–0.8) | — |
| Subtotal: Case series (I-squared = 0.0%; p = 0.709) | | | | 0.6 (0.5–0.7) | |
| Overall (I-squared = 85.1%; p = 0.000) | | | | 0.6 (0.4–0.7) | |

Notes: CI = confidence interval; EGRCIBD-Japan = Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan.

**Appended Data Table for Figure 10.9**

| Study | Disease | Country | Smoking definition | Number of cases | Effect size (95% CI) | Adjustments |
|---|---|---|---|---|---|---|
| Funakoshi 1987 | Crohn's disease | Japan | Current at symptom onset | 25 | 0.5 (0.2–1.4) | Age |
| Firouzi 2006 | Crohn's disease | Iran | Current at diagnosis | 46 | 0.4 (0.2–1.2) | Age, gender, tonsillectomy or appendectomy, non-steroidal anti-inflammatory drugs, oral contraceptives of hormone replacement therapy |
| Subtotal: Crohn's disease (I-squared = 0.0%, p = 0.771) | | | | | 0.5 (0.2–1.0) | |
| Funakoshi 1987 | Ulcerative colitis | Japan | Current at symptom onset | 105 | 0.5 (0.3–0.8) | Age |
| EGRCIBD-Japan 1994 | Ulcerative colitis | Japan | Current at diagnosis | 101 | 0.7 (0.2–2.0) | Age; gender; location, region or center; alcohol |
| Nakamura 1994 | Ulcerative colitis | Japan | Current at symptom onset | 300 | 0.3 (0.2–0.5) | Age, gender, alcohol |
| Firouzi 2006 | Ulcerative colitis | Iran | Current at diagnosis | 382 | 0.2 (0.1–0.3) | Age, gender, tonsillectomy or appendectomy, non-steroidal anti-inflammatory drugs, oral contraceptives of hormone replacement therapy |
| Jiang 2007 | Ulcerative colitis | China | Current at diagnosis | 155 | 0.3 (0.2–0.6) | Age, gender, family history of inflammatory bowel disease, former smoking, tonsillectomy or appendectomy, alcohol, coffee or tea, diet |
| Subtotal: Ulcerative colitis (I-squared = 60.9%, p = 0.037) | | | | | 0.3 (0.2–0.5) | |
| Overall (I-squared = 48.7%, p = 0.069) | | | | | 0.3 (0.2–0.5) | |

Source: Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan (EGRCIBD).
Note: CI = confidence interval.